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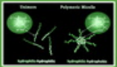
Polyelectrolytes and Polyzwitterions

Synthesis, Properties, and Applications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EDITED BY
Andrew B. Lowe and Charles L. McCormick

Polyelectrolytes and Polyzwitterions

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ACS SYMPOSIUM SERIES **937**

Polyelectrolytes and Polyzwitterions

Synthesis, Properties, and Applications

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Foreword

The ACS Symposium Series was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

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Preface

Polymers come in many shapes and sizes—literally! Of the plethora of materials designed and synthesized during the past 100 years or so, those containing charged or potentially charged functional groups represent an extremely important class of macromolecule. Such materials, of course, are naturally occurring and encompass examples of the fundamental building blocks of life including proteins, the nucleic acids, and certain carbohydrates. Synthetic analogs of such species have likewise found a variety of commercial applications including enhanced oil recovery, cosmetics, paper making, stabilizers in emulsions formulations, drug delivery vehicles, gene delivery vehicles, contact lenses, and as coatings for blood filtration devices to name only a few.

This book was developed from the American Chemical Society (ACS) Symposium *Polyelectrolytes and Polyzwitterions: Synthesis, Properties, and Applications* presented at the ACS 228th National Meeting held in Philadelphia, Pennsylvania in August of 2004. The aim of this ACS Symposium Series book is to give the reader an appreciation of the state-of-the-art with respect to the synthesis of polyelectrolytes and polyzwitterions as well as to highlight solution properties–theory as some applications for such synthetic materials. This book comes at a time when quite amazing advances are being made—it seems almost on a weekly basis—with respect to the synthesis of these species. With the development of controlled free radical polymerization in its various guises during the past decade as well as other synthetic methodologies, the polymer chemist working in synthesis has an ever-growing toolbox with which to prepare novel, well-defined materials with generally excellent control of the molecular characteristics. With the ever

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increasing demand for highly functional materials for specialty applications, such techniques are proving invaluable in both academic as well as commercial settings.

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Chapter 1

Polyelectrolyte Solutions: Phenomena and Interpretation

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Introduction

When Herman Staudinger first suggested a study of macromolecules with large numbers of ionic substituents appended to the polymer backbone, he wrote (in 1932) that "there are few natural products of high molecular weight for which work on a more easily analyzable model substance appears as necessary as for proteins" (1). He chose poly(acrylic acid) (PAA) for the first such study and Staudinger's student W. Kern published in 1938 and 1939 a series of papers on the behavior of PAA solutions (2). He uncovered a number of the characteristic features of polyelectrolyte solutions: The apparent ionization constant of the carboxyls decreased sharply with the degree of ionization, neither the titration curve nor the electrical conductivity changed with the length of the chain molecule and the solution viscosity increased sharply with the degree of neutralization, but decreased on the addition of simple electrolytes. However, the interpretation of the data was rather far-fetched since Staudinger was so committed to thinking of polymer molecules as rigid rods, that Kern did not dare to see in the increasing solution viscosity, as the PAA was being ionized, evidence for the expansion of the molecular chains.

Ten years after Kern's publications Fuoss, who had long worked on the physical chemistry of electrolyte solutions, coined the term "polyelectrolyte" and suggested (3) that the characteristic phenomena of their solutions should best be studied on polymers whose charge is independent of pH and the ionic environment ("strong polyelectrolytes"), such as quaternized poly (vinyl pyridine) and sulfonated polystyrene.

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Polyion expansion.

W. Kuhn, who had formulated the statistics of randomly kinked polymer chains, was first to attempt with his collaborators to formulate a theory of the expansion of a chain carrying evenly spaced ionizable groups (4). He argued that the *a priori* distribution of end-to end displacements **h** for uncharged chains would have to be weighted by $\exp\{-G_{el}(\mathbf{h})/kT\}$ where $G_{el}(\mathbf{h})$ was the electrostatic energy corresponding to a given value of **h**, obtained by summing over all binary interactions between polymer-bound ionic charges. He assumed that at "sufficient dilution" the counterions would be removed from the polymer domain, so that they would not affect G_{el}. This assumption was found later to be wrong. Also, the model was incorrect in neglecting the way in which the polymer charges affect the distribution of chain conformations for a given value of the chain-end displacement **h**. Later, Katchalsky and Lifson took account of the screening of the repulsion of the polymer-bound charges by the counterion atmosphere (5), but their model also overestimated the extent to which the polymer chain was expanding with an increasing charge density.

Flory considered the case of polyelectrolytes in a solution of simple electrolytes, where the polymer coil may be pictured as occupying a spherical volume with the counterions neutralizing most of the polymer-bound charges, so that the polymer should behave like an ionized gel particle subject to the Donnan equilibrium (6). The expansion of the coil is then due to the osmotic forces due to the excess of mobile ions within the polymer domain and the hydrodynamic volume of the polymer coil bears the same relation to the intrinsic viscosity as in uncharged polymers. Flory represented the polyelectrolyte expansion as a function of the ionic strength, but this was not acceptable for 2:1 electrolytes, since the polyion is highly sensitive to the counterion charge, but insensitive to the charge of byions as pointed out by Fixman (7).

Polyions, such as ionized cellulose derivatives, behave like "worm-like chains" whose flexibility is characterized by their "persistence length". Odijk (8) suggested that on charging such semiflexible chains the persistence length may be represented by $P = P_t + P_e$, where P_t is an intrinsic value of the chain molecule and P_e, the electrostatic contribution, reaches a limit when the polymer charge leads to counterion condensation.

In the absence of simple salts, the reduced viscosity of flexible polyions increases with an increasing dilution of the solution, and it cannot be extrapolated to zero concentration to yield an "intrinsic viscosity". Fuoss

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suggested that the intercept of a linear plot of the inverse reduced viscosity against the square root of the polyelectrolyte concentration can be used to characterize the chain expansion (9) and this empirical relation was widely used. However, Eisenberg and Pouyet showed (Fig. 1) that the reduced viscosity passes, in the absence of simple electrolytes, through a maximum and then declines sharply on further dilution (10). This indicates that after the polyion reaches its maximum extension, the decrease of intermolecular electrical interactions is responsible for the decline of the reduced viscosity with a decreasing polyion concentration.

If a sufficient concentration of simple salts is added to the polyelectrolyte solution, plots of the reduced viscosity against concentration become linear and the Mark-Houwink relationship can be used to estimate from the intrinsic viscosity the molecular weight of the polyion.

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Counterion distribution.

In 1951 the distribution of counterions was calculated for a model in which the polyions were represented by parallel rods at a fixed spacing in a salt-free aqueous solution (11). An explicit solution of the Poisson-Boltzmann equation led to the conclusion that a substantial fraction of the counterions would remain in the vicinity of the polyion even at extreme dilution (Fig. 2). Later, it was suggested by Imai and Onishi (12) that a rod-like polyion cannot sustain a charge density exceeding a critical value. This concept was elaborated by Manning (13) who concluded that the critical charge density is **DkT/e**, where **D** is the dielectric constant of the solvent and **e** the charge of the electron. For instance, in the titration of poly (acrylic acid), where the critical charge density corresponds to a degree of neutralization of 34%, further addition of base should lead to the "condensation" of counterions on the polyion leaving the polyion charge unchanged. A variety of experimental evidence supports Manning's theory. Thus, in salt-free polyelectrolyte solution the product of the osmotic coefficient and the polymer charge density becomes constant under conditions where counterion condensation would be expected (14). However, as will be discussed later, some experimental data seem to cast doubt on the assumptions of the theory.

Ionization equilibria.

The dependence of the ionization constant of a weak polyelectroyte on the polymer charge density may be represented by

$$pK_{app} = pK_0 + 0.43\ \Delta\ G_{el}\ (\alpha)\ /\ RT$$

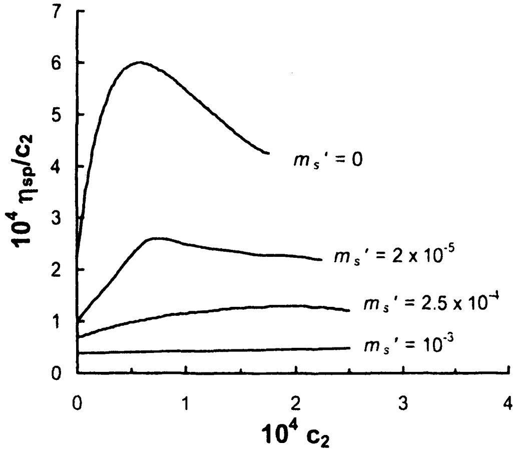

Figure 1. Reduced viscosity plots of poly(N-butyl-4-vinylpyridium) bromide with various concentrations of added sodium chloride ($m_{s'}$).

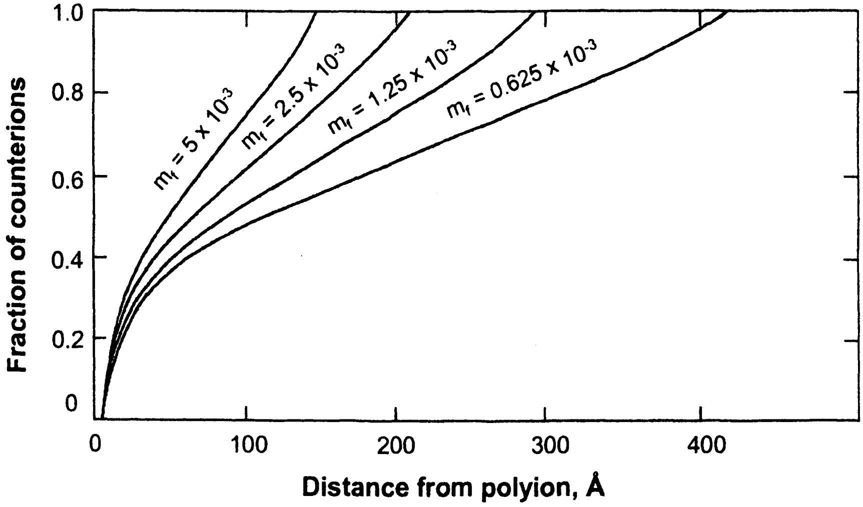

Figure 2. Integral counterion distribution around rodlike polyions. (Charge density 0.5/nm;)

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where $\Delta G_{el}(\alpha)$ is the electrostatic free energy required to remove a mole of protons from a polymer with a degree of ionization α. For poly (acrylic acid) (PAA), Mandel (15) found (Fig. 3) that pK could be represented as a quadratic function of α. Thus, the pK keeps increasing beyond the point where counterion condensation should keep the polyion charge density constant. Manning dealt with this difficulty by assuming that the condensed counterions are "territorially bound" so that they do not affect the ionization equilibrium (16).

In early attempts to compare experiment and theory poly (methacrylic acid) (PMA) was used as the subject of investigation. This was a historical accident, since methacrylic acid could easily be obtained from the poly (methyl methacrylate) used for airplane windows in World War II (17). It was realized only much later that the behavior of PMA is anomalous. Whereas the pK of PAA rises monotonously with increasing ionization, the pK of PMA passes, after an initial rise, through a plateau before resuming its increase (18). Mandel et al. interpreted this behavior as reflecting a local conformation transition from a more contracted, less ionized to a more expanded, more highly ionized sequence with the same linear charge density (19). Crescenzi et al. (20) compared the calorimetric titration of PAA and PMA and found a sharp endotherm for PMA in the range where the pK exhibits a plateau (Fig. 4).

Before this transition is completed, PMA forms clusters around small aromatic species. Since the fluorescence of many dyes is quenched by contact with water, the clustering of PMA around a dye leads to a sharp increase in emission intensity which, as seen in Fig. 5, drops precipitously in the pH range where the pK exhibits a plateau (21). Another evidence for PMA clustering was provided by the reduction of the conformational mobility of binaphthyl residues attached to the polymer chain (22).

Reaction kinetics.

A variety of kinetic phenomena have been studied in polyelectrolyte solution. These may be subdivided as follows:

(a) Rate of chain expansion following ionization. This was studied for PMA carrying dansyl labels, taking advantage of the dramatic increase in the fluorescence intensity of the dansyl group when its contact with water is prevented by the clustering of short PMA segments around the fluorophore. Thus, the rate of chain expansion could be followed in a stopped-flow apparatus after mixing an acidic PMA solution with a buffer of higher pH when the disruption of the PMA clusters leads to a drop in the dansyl emission intensity (23).

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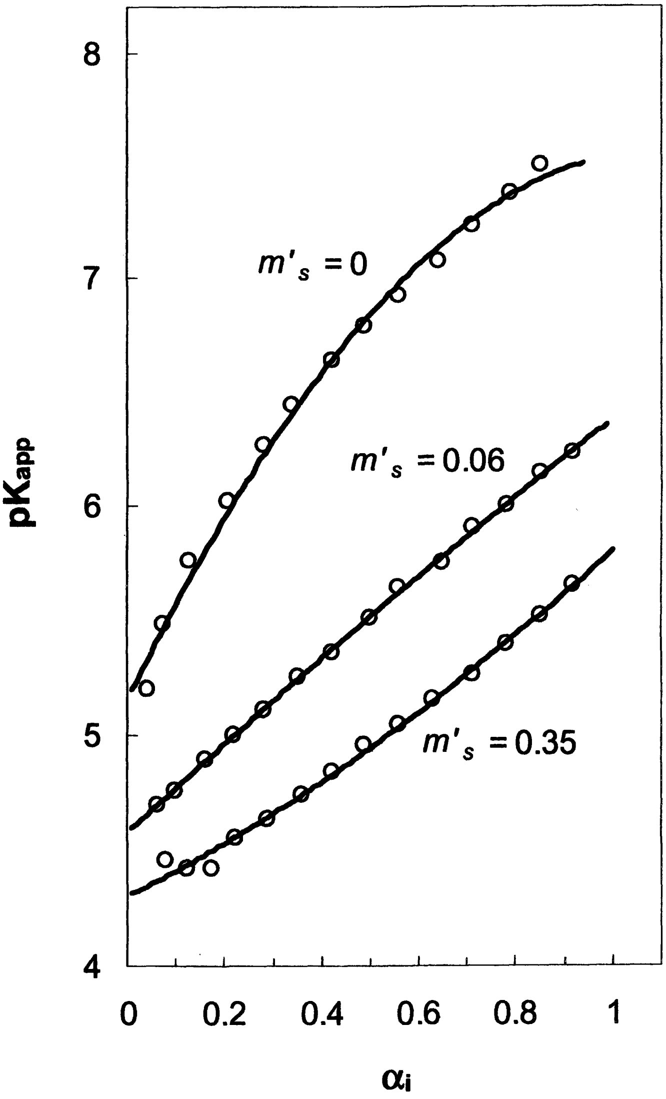

Figure 3. Dependence of pK_{app} *of poly(acrylic acid) (M.W. = 7.9 x* 10^5*; conc.* 10^{-3}*N) on the degree of ionization* α_i*.*

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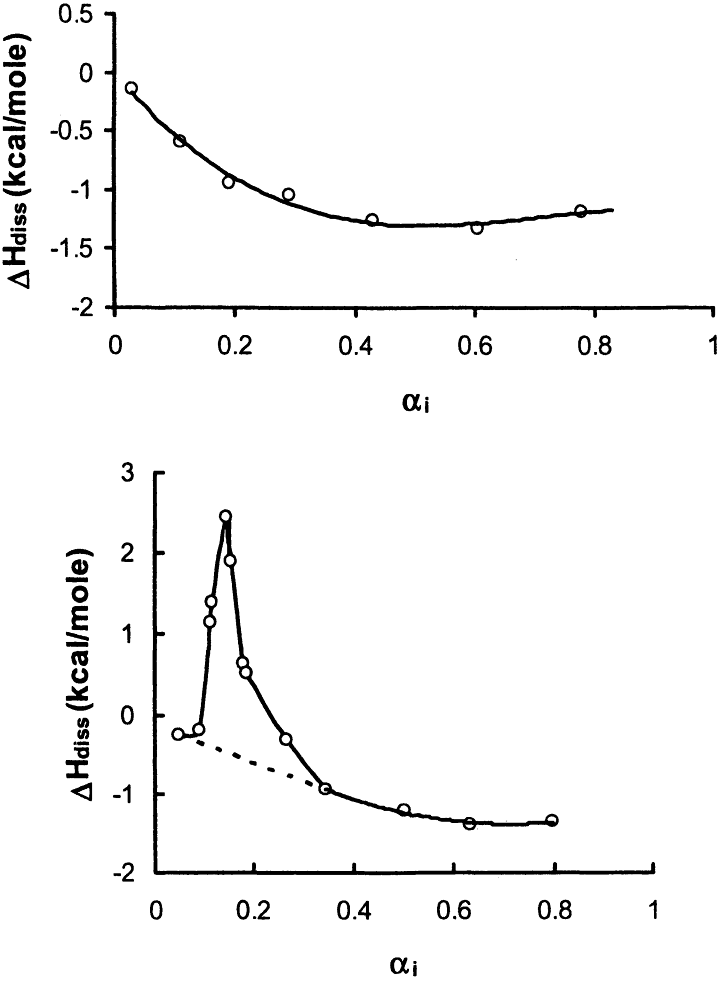

Figure 4. Dependence of the enthalpy of dissociation of polycarboxylic acids on the degree of ionization α_i in the absence of added salts. (O) 0.065N poly(acrylic acid), (□) poly(methacrylic acid).

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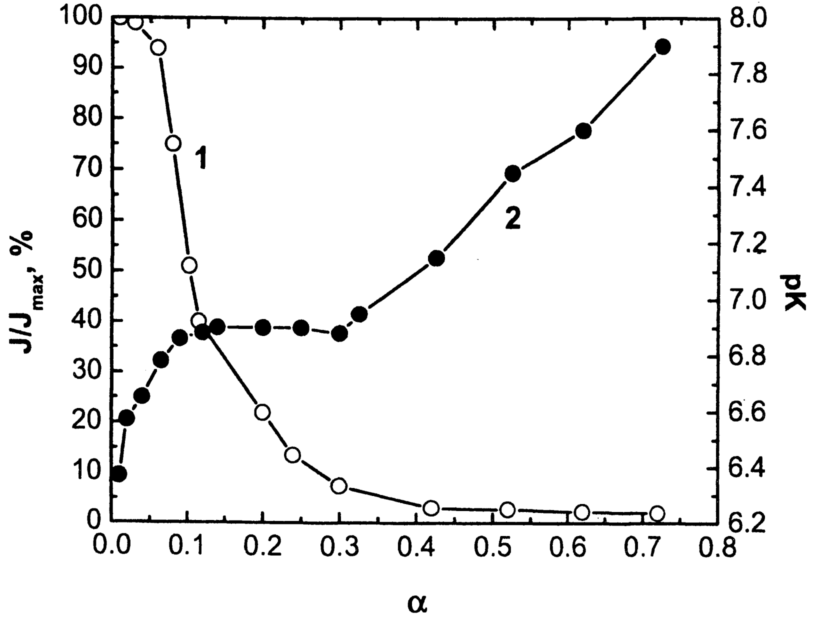

Figure 5. The dependence of the fluorescence intensity of auramine (1) and the pK (2) on the degree of ionization of PMA.

(b) Intramolecular reactions of polyions. It was expected that a hydroxyl-ion-catalyzed hydrolysis of an ester group attached to a polyion should be repressed because of the repulsion of the OH ions from the polyion domain. However, it was found that the hydrolysis of nitrophenyl esters is orders of magnitude faster at neutral pH when the ester is attached to PAA (24). This is because the reaction rate is determined by the attack of a neighboring ionized carboxyl on the ester, forming a transitory anhydride. If the nitrophenyl ester was attached to PMA, the hydrolysis was biphasic, depending on the relative configurations of the carbons to which the carboxylate and the ester were attached (25).

(c) Polyion reactions with small ions. In 1953 Deuel et al. studies the OH catalyzed hydrolysis of pectins, the partially esterified derivatives of polygalacturonic acid and found that the apparent second-order reaction rate constant falls off rapidly with the progress of the reaction. This rate was also accelerated on addition of salts (26). These phenomena were clearly due to the repulsion of the OH ion from the polymer, which was decreased when salt was added. A similar effect was reported for a copolymer of N-azobenzeneacrylamide with acrylic or methacrylic acid, where the OH catalyzed cis-trans isomerization of the azobenzene moiety was inhibited (27).

(d) Effect of polyions on bimolecular reactions of small ions. Since counterions are concentrated in the polymer domain whereas byions are repelled, the reaction rate of a cationic with an anionic reagent is expected to be decreased in polyelectrolyte solutions. The theory and experimental verification of this effect was presented in a study of the OH catalyzed hydrolysis of cationic esters (28). On the other hand, reactions of two cationic reagents, both attracted to a polyion, are accelerated. This was first demonstrated (Fig. 6) in a study of the effect of poly (vinyl sulfonic acid) on the quenching of uranyl fluorescence by Fe^{++} (29). At low Fe^{++} concentrations the polyanion enhances sharply the quenching efficiency, but when the concentration of the bivalent ions exceeds the normality of the polyanion, the uranyl ion is displaced from the polymer domain and an increase of the quencher concentration leads to an increase of the emission intensity. Another dramatic effect was observed (Fig. 7) in the reaction of two bivalent ions

$$Co(NH_3)_5Cl^{2+} + Hg^{2+} + H_2O = HgCl^+ + Co(NH_3)_5H_2O^{3+}$$

which was accelerated by several orders of magnitude in the presence of polysulfonic acids (30).

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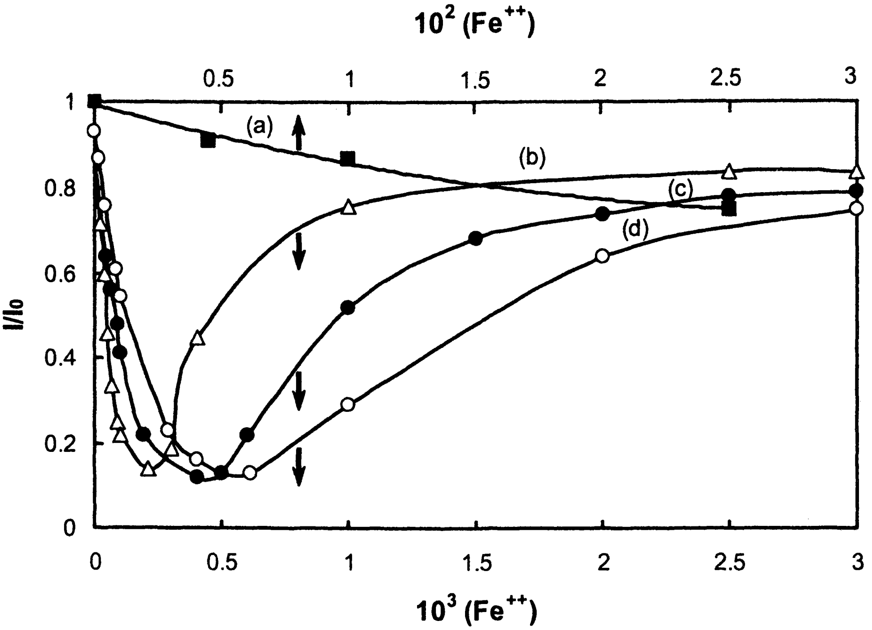
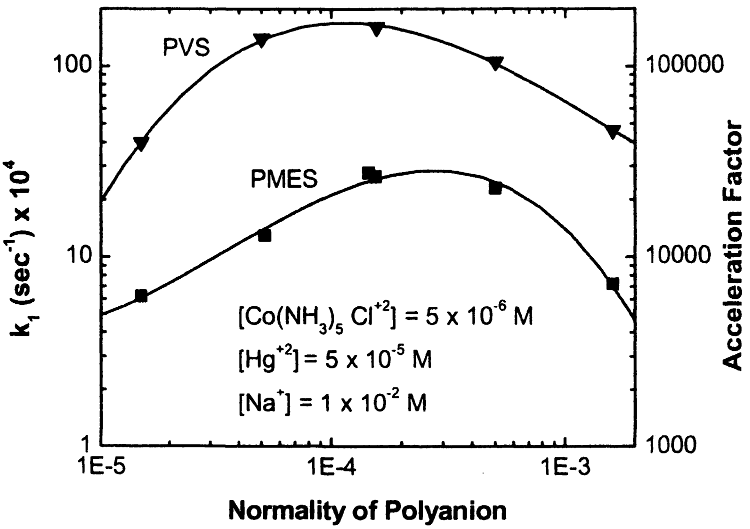
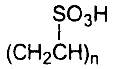


Figure 6. Effect of PVS on the quenching of quinine fluorescence by Fe^{++} PVS normality: (a) 0; (b) 0.001 (c) 0.002 (d) 0.003.

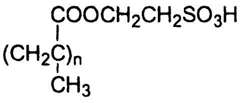


$[Co(NH_3)_5Cl]^{2+} + Hg^{2+} = [Co(NH_3)_5H_2O]^{3+} + HgCl^{+}$



$(CH_2CH(SO_3H))_n$

PVS



$(CH_2C(CH_3)(COOCH_2CH_2SO_3H))_n$

PMES

Figure 7. Polyion catalysis of the reaction of two doubly charged counterions.

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Amphoteric polyelectrolytes.

Random copolymers of acidic and basic monomers were first prepared from 2-vinylpyridine and methacrylic acid (VP-MA) (31). As expected, the polymer chains behaved in acid solution as polycations and in basic solution as polyanions. In the range around the isoelectric point (IEP) they were insoluble in water. This contrasted with the behavior of copolymers of methacrylic acid with diethylaminoethyl methacrylate (MA-DMAEMA) which were water soluble over the entire range of pH (32). In isoelectric solution addition of salt led to an increase of viscosity (as might have been expected, since the added salts shields the attraction between the cationic and anionic monomer residues). The difference between the behavior of the two copolymers can be explained as follows: In the VP-MA copolymer the pK of pyridinium is similar to that of the carboxyl group, so that at the IEP a substantial fraction of the pyridine and carboxyl is unionized. By contrast, in the MA-DEAMA copolymer, hydrogen ions are bound many order of magnitude more strongly to the amino group than to carboxylate, so that the polymer is zwitterionic in isoelectric solution. Another zwitterionic polymer, containing monomer residues with sulfonic acid and quaternary ammonium residues, was found to be soluble only in the presence of added salt (33).

The behavior of block copolymers containing anionic and cationic blocks seems to depend on their chemical nature. At the IEP, the MA-DMAEMA block copolymer was found to be water insoluble, (34) but the styrene sulfonate block copolymer with 2-vinyl pyridine was soluble (35).

Another type of amphoteric polyelectrolyte is formed by the attachment of zwitterionic substituents to the polymer chain. This was first exemplified by poly (4-vinyl pyridine betaine) (36). Such polymers are frequently insoluble in water, but dissolve on addition of salts. The solubilizing power does not seem to be sensitive to the cation, but increases with the radius of the anion. The solution viscosity increases with the concentration of the added salt (37). Near monodisperse zwitterionic polymers have been prepared by the polymerization of sulfobetaine monomers in aqueous media *via* RAFT (38).

Curiously, one aspect of zwitterionic polyelectrolytes does not seem to have been explored. It is known that small zwitterions, such as glycine, produce a sharp increase in the dielectric constant of water solutions (39). It would then be of great interest to find whether the high concentration of betaine residues in the vicinity of a polymer chain leads to effects which can be ascribed to a high local dielectric constant.

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Ionized polymers in non-aqueous media.

Ionomers are nonpolar chain molecules carrying on a small portion of their monomer residues ionized substituents with their counterions. Their behavior reflects the high stability of ion-pairs and their tendency to dimerize in media of low dielectric constant. This dimerization is intramolecular in highly dilute solution leading to a chain contraction, but it leads at higher solution concentrations to intermolecular association and a sharp increase in solution viscosity (40, 41).

Fluorescence effects attending the transfer of counterions between ionomer molecules could be monitored in a stopped-flow apparatus. It was found that the rate constant of proton transfer in a highly dilute toluene solution from a methyl methacrylate copolymer with 1% of p-aminostyrene to a similar copolymer with 1-2% of a comonomer carrying an aliphatic amine decreased with the size of the ionomers. This demonstrated for the first time that the "excluded volume effect" seen in the osmotic behavior of polymer solutions also affects reaction kinetics (42). In another approach, two portions of a slightly sulfonated polystyrene were neutralized with different fluorescent counterions and the counterion exchange was monitored by the increasing non-radiative energy transfer between them (43).

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An unexpected effect was found in the fluorescence behavior in toluene solution of butyl methacrylate copolymers with a comonomer carrying ionized naphthoic acid residues with alkali counterions (44). When the copolymer contained very few of these fluorescent monomer residues, the emission spectrum exhibited only one emission peak. However, as the content of these residues increased, a second emission peak was observed which become more intense as the first one became weaker. It was concluded that the two emissions are due to isolated ion-pairs and ion-pair dimers. The fluorescence spectra depended on the nature of the alkali counterions reflecting the difference between their ion-pair dimerization equilibrium.

The behavior of a non-aqueous solution of polyelectrolytes carrying an ionized group on each monomer residue is of particular interest. Mandel and his collaborators studied the titration of PAA in methanol using a variety of experimental techniques and found that the polymer first expanded, but then collapsed with an increasing degree of neutralization (45). Whereas the collapse was gradual with Li counterions, it occurred abruptly with only 10% of the carboxylates ionized when Na was the counterion. We have recently reinvestigated this phenomenon with titration of PAA and PMA in methanol using solution viscosity and ^1H NMR spectroscopy (46). We concluded that the polyion collapse is due to the attraction between the ion-pairs formed in the medium of the relatively low dielectric constant, which also inhibits the conformational mobility of the polymer chains as demonstrated by the broadening and eventual disappearance of the NMR spectrum. Fig. 8 shows the difference between the behavior of PAA and PMA. We believe that this is due to the lower effective dielectric constant in the vicinity of the PMA chain. While Manning's theory of counterion condensation (13) assumes that the process is governed by the dielectric constant of the solvent, there is important evidence that the effective dielectric constant is much lower in the vicinity of organic solutes. It should then be lower close to the less polar PMA chain. The difference between the behavior of the polyions with Li and Na counterions is tentatively ascribed to the much stronger tendency of Na+ ion-pairs to dimerize in an ion-pair solvating medium.

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Inter-polyelectrolyte Complexes.

The mixing of stoichiometric polyanions and polycations leads to the precipitation of a inter-polyelectrolyte complex (IPEC). However, when one of the polyions is in excess, the complex is water soluble; such non-stoichometric inter-polyelectrolyte complexes have been intensively studied by Kabanov and his collaborators. The complex of an excess of a pyrenyl-labeled Na salt of PMA (PMA*) with poly (N-ethylpyridinium bromide) (PMA*-PEPB) dissociates on addition of a critical salt concentration of simple salts as evidenced by the elimination of the quenching of the pyrenyl fluorescence and this critical salt concentration increases with the length of the polyion chains (47). When solutions of PEP were mixed with a solution of block copolymer of poly (ethylene oxide) and sodium methacrylate, the IPEC was soluble even when it contained stoichiometric anionic and cationic groups (48). It self-assembled into micelles with a IPEC core and a PEO corona.

The kinetics of the interchange of one component of the IPEC complex was studied by mixing a solution of the PEPB-PMA complex with a solution of PMA* where the progress of the interchange could be monitored by the quenching of the pyrenyl fluorescence (49). When the PMA could accommodate only one PEPB chain, the process followed second order kinetics. The rate constants increased sharply on addition of electrolyte and with a decreasing degree of quaternization of the PEPB but were independent of the length of the interaction polyions.

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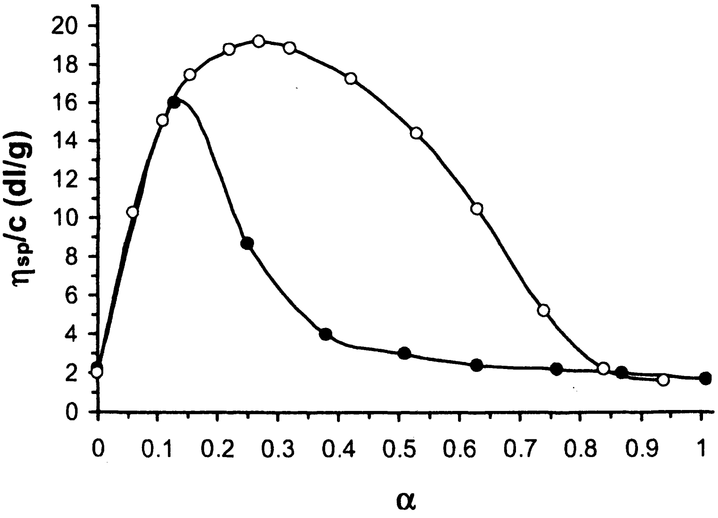

Figure 8. Reduced viscosity (η_{sp} / c) of 0.015M PAA (O) and 0.015M PMA (●) in methanol titrated with $LiOCH_3$.

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Chapter 2

Amphiphilic Polyelectrolytes: Characterization of Associative Properties and Self-Assembled Nanostructures in Water

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Amphiphilic polyelectrolytes undergo hydrophobically driven self-association in water to form well-defined spatial structures on a nanometer scale (nanostructures) depending on their macromolecular architectures. This chapter is a tutorial overview of amphiphilic polyelectrolytes of various architectures focusing on analytical techniques with different length scales for the characterization of their nanostructures.

Over the past two decades, amphiphilic polyelectrolytes that possess both charges and hydrophobes along or pendent to the polymer backbone have attracted considerable attention mainly because of interest in their self-assembling properties and their nanostructures. The type of the nanostructures depends primarily on whether hydrophobic associations occur within the same polymer chain or between different chains, which strongly depends on the macromolecular architecture. Thus, one can prepare an amphiphilic polyelectrolyte of given properties by properly designing its polymer structure.

Aqueous solutions of amphiphilic polymers exhibit unique rheological properties as well as phase behavior. Thus, practical interest in amphiphilic polyelectrolytes arises from their potential in a variety of commercial applications such as associative thickeners, rheology modifiers, emulsifiers, stabilizers of dispersions, solubilizers, and flocculants (*1*). In addition, solution properties of some of amphiphilic polyelectrolytes are sensitive to changes in external conditions such as ionic strength, shear stress, temperature, and pH.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

because of their potential ability to capture and release materials, which may find pharmaceutical or environmental application (*2*).

This chapter will present a tutorial overview of the self-assembling of amphiphilic polyelectrolytes with an emphasis put upon characterization methods with varying dimensional scales.

General Synthetic Approaches for Amphiphilic Polyelectrolytes

A large number of self-associating amphiphilic polyelectrolytes with various sequential structures have so far been synthesized by various methods. One can think of two practical ways to covalently introduce hydrophobes into a polyelectrolyte, i.e., by random, alternating, block or graft copolymerization of an electrolyte monomer and a hydrophobic monomer or by chemical modification of a precursor polyelectrolyte with a reactive, hydrophobic molecule ("post-polymerization reaction" or "polymer reaction").

Block Copolymerization.

Block polyelectrolytes have been synthesized by living anionic polymerization of monomers followed by post reaction such as hydrolysis, quaternization or sulfonation. Some of the block copolymers synthesized by this technique are listed in Chart 1. For example, in order to obtain a poly(methacrylic acid) block, one can use *tert*-butyl methacrylate (*3*) or trimethylsilyl methacrylate (*4*). After the polymerization, the protecting group is removed by hydrolysis. By sequential addition of monomers using initiators capable of producing chains with two living ends, e.g., sodium naphthalene, multiblock polymers can be obtained.

Although living anionic polymerization is the most suitable method for the preparation of block copolymers free from homopolymers and with low polydispersity, a disadvantage is the fact that only a limited type of monomers can undergo controlled anionic polymerization without termination or chain transfer. Recently, controlled radical polymerization (CRP) techniques including atom transfer radical polymerization (ATRP) (*5*), reversible addition fragmentation chain transfer (RAFT) (*6*), and nitroxide-mediated free radical polymerization (*7*) have been extensively studied and found to be extremely useful for the synthesis of block polyelectrolytes. An advantage for CRP is that CRP is much less sensitive to impurities than living anionic polymerization. Furthermore, CRP methods allow one to synthesize block copolymers that cannot be synthesized by any other methods. Some of the examples of block copolymers synthesized by CRP methods are listed in Chart 2.

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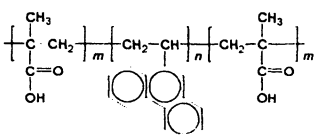
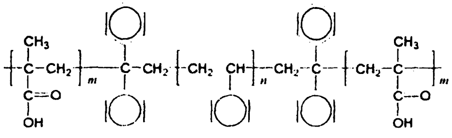
Chart 1. Amphiphilic Block Polyelectrolytes by Living Anionic Polymerization



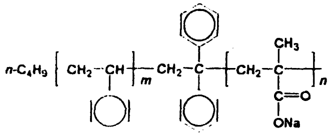
$m = 77$, $n = 43$
$m = 54$, $n = 23$
$m = 53$, $n = 16$
$m = 23$, $n = 7$

(*27*)



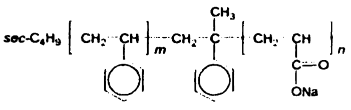
M_w = 16 500, PS block content = 45 wt %

(*28*)



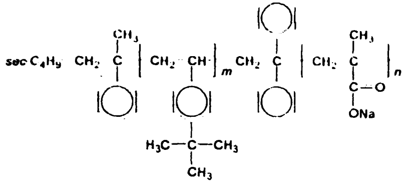
$m = 170$, $n = 9$ or 25
$m = 440$, $n = 7$, 18, or 40
$m = 1100$, $n = 6$, 21, 42, or 59

(*29*)



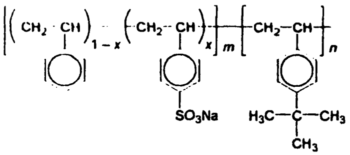
$m = 6$, $n = 400$ or 1000
$m = 11$, $n = 350$ or 1030
$m = 14$, $n = 270$ or 620
$m = 23$, $n = 300$, 780, or 1400
$m = 28$, $n = 330$ or 1560
$m = 40$, $n = 520$ or 2420
$m = 86$, $n = 390$ or 900
$m = 110$, $n = 380$ or 2360

(*30*)



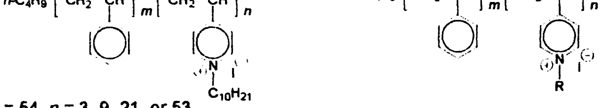
M_n = 10 400 (before hydrolysis)
M_n of PtBS block = 4 000

(*31*)



$m = 404$, $n = 26$, $x = 0.89$
$m = 757$, $n = 27$, $x = 0.87$

(*32*)



$m = 54$, $n = 3$, 9, 21, or 53
$m = 180$, $n = 11$, 29, 73, or 190
$m = 260$, $n = 13$, 29, 71, 120, or 240
$m = 480$, $n = 13$, 34, 79, or 200

R = CH_3, C_4H_9, C_6H_{13}, $C_{10}H_{21}$, or $C_{18}H_{37}$
$m = 260$, $n = 240$

(*33*)

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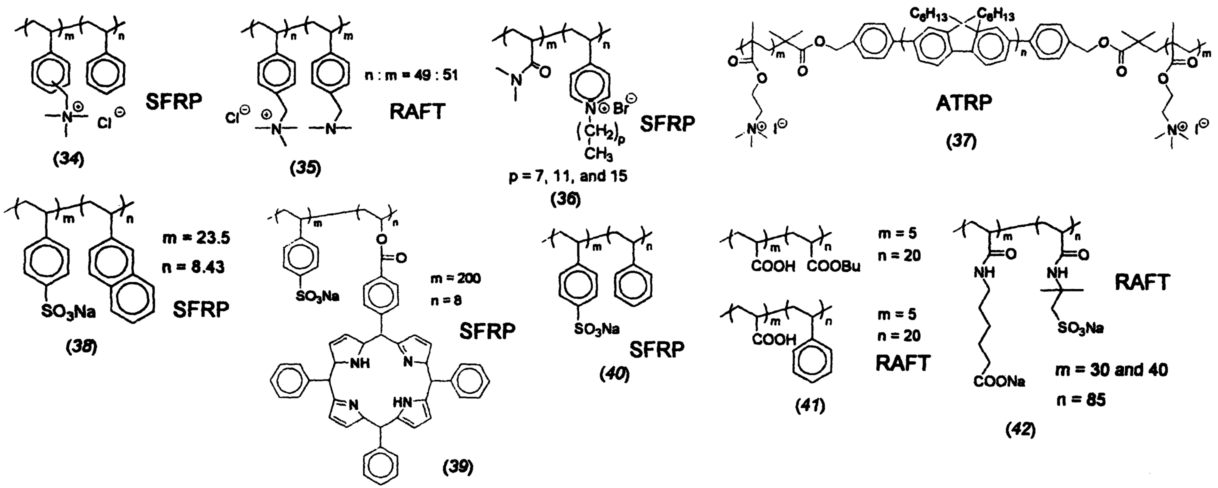
Chart 2. Amphiphilic Block Copolymers by Controlled Radical Polymerization


(34)
SFRP
(35)
n : m = 49 : 51
RAFT
p = 7, 11, and 15
(36)
SFRP
ATRP
(37)
m = 23.5
n = 8.43
SFRP
(38)
m = 200
n = 8
SFRP
(39)
SFRP
(40)
m = 5
n = 20
m = 5
n = 20
RAFT
(41)
RAFT
m = 30 and 40
n = 85
(42)

SFRP = Stable Free-Radical Polymerization, RAFT = Reversible Addition-Fragmentation Chain Transfer Radical Polymerization, ATRP = Atom Transfer Radical Polymerization

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Random Copolymerization.

A large number of amphiphilic random copolymers of ionic and hydrophobic monomers have been prepared by free radical polymerization. Some of these examples are listed in Chart 3. The sequence distribution of the monomer units is an important factor to influence their association behavior (*8*). Homogeneous solution polymerization may yield copolymers with statistical sequence distributions depending on monomer reactivity ratios whereas micelle or emulsion polymerization may give copolymers with blocky sequences (*8,9*). Most commonly used as ionic monomers are (meth)acrylic acid and 2-(acrylamido)-2-methylpropanesulfonic acid (AMPS). Some of the examples for carboxylic acid-based and AMPS-based amphiphilic random copolymers are presented in Charts 3 and 4, respectively.

Amphiphilic polyelectrolytes with random sequence distributions can also be prepared by homo- or copolymerization of polymerizable ionic amphiphiles, often referred to as "surfmers" (*10*).

Alternating Copolymerization.

Various amphiphilic polyelectrolytes have been synthesized base on so-called "alternating" copolymerization using maleic anhydride followed by hydrolysis. Some examples are listed in Chart 5. Dubin and Strauss (*11*) were the first to reveal that alternating copolymers of maleic acid and butyl and hexyl vinyl ethers undergo a conformational transition from a compact to extended structure, and *vice versa*, in a narrow pH window whereas the copolymer with octyl vinyl ether adopts a "hypercoiled" structure independent of pH. An advantage of the maleic anhydride copolymers is that hydrophobes and charges can be introduced by coupling reaction of the maleic anhydride unit with alkylamines followed by hydrolysis.

Chemical Modification.

Strauss and Jackson (*12*) were the first to synthesize "polysoaps" by quaternization of poly(2-vinylpyridine) with *n*-dodecyl bromide (Chart 6), and they demonstrated that the polymer adopted a compact conformation due to aggregation of the long aliphatic side chains in water. Amphiphilic polyelectrolytes based on polyssacharides have been synthesized by polymer reaction. In Chart 6 are presented some of the examples of anionic and cationic celluloses modified with hydrophobic molecules.

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Chart 3. Carboxylic Acid-Based Amphiphilic Random Copolymers by Radical Polymerization

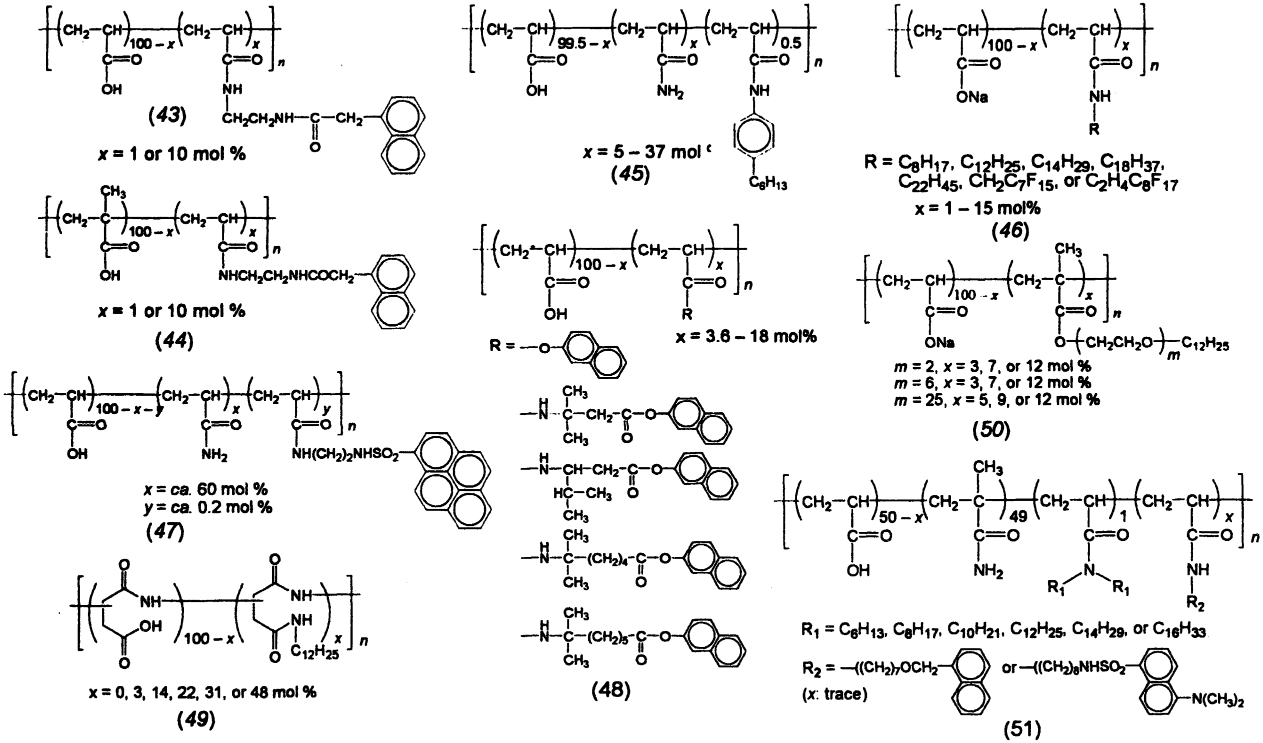
(43)
x = 1 or 10 mol %
x = 1 or 10 mol %
(44)
x = ca. 60 mol %
y = ca. 0.2 mol %
(47)
x = 0, 3, 14, 22, 31, or 48 mol %
(49)
x = 5 – 37 mol %
(45)
x = 3.6 – 18 mol%
R =
(48)
R = C8H17, C12H25, C14H29, C18H37, C22H45, CH2C7F15, or C2H4C8F17
x = 1 – 15 mol%
(46)
m = 2, x = 3, 7, or 12 mol %
m = 6, x = 3, 7, or 12 mol %
m = 25, x = 5, 9, or 12 mol %
(50)
R1 = C6H13, C8H17, C10H21, C12H25, C14H29, or C16H33
R2 = —((CH2)7OCH2— or —((CH2)8NHSO2—
(x: trace)
(51)

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Chart 4. AMPS-Based Amphiphilic Random Copolymers by Radical Polymerization

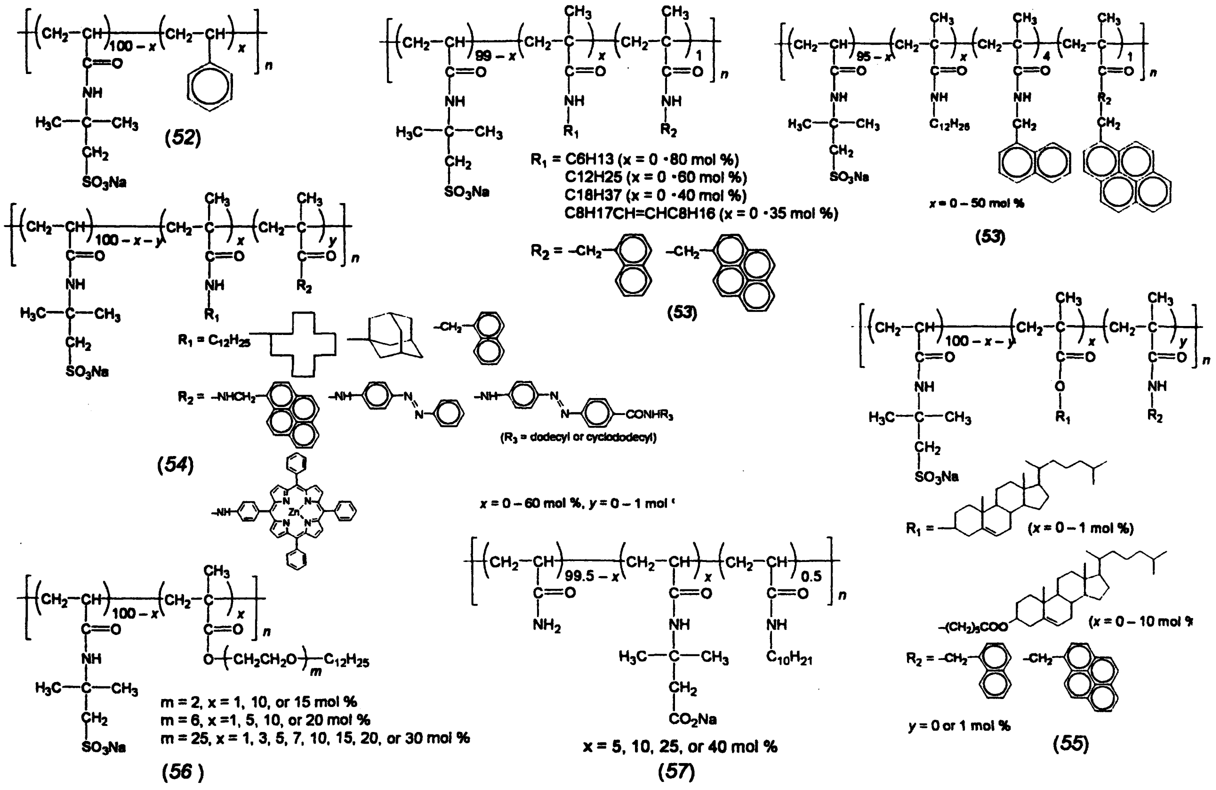
(52)
R₁ = C6H13 (x = 0 -80 mol %)
C12H25 (x = 0 -60 mol %)
C18H37 (x = 0 -40 mol %)
C8H17CH=CHC8H16 (x = 0 -35 mol %)
R₂ =
(53)
x = 0 – 50 mol %
(53)
R₁ = C₁₂H₂₅
R₂ = -NHCH₂
(R₃ = dodecyl or cyclododecyl)
(54)
x = 0 – 60 mol %, y = 0 – 1 mol %
R₁ =
(x = 0 – 1 mol %)
(x = 0 – 10 mol %)
R₂ =
y = 0 or 1 mol %
(55)
m = 2, x = 1, 10, or 15 mol %
m = 6, x = 1, 5, 10, or 20 mol %
m = 25, x = 1, 3, 5, 7, 10, 15, 20, or 30 mol %
(56)
x = 5, 10, 25, or 40 mol %
(57)

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Chart 5. Maleic Anhydride-Based "Alternating" Copolymers

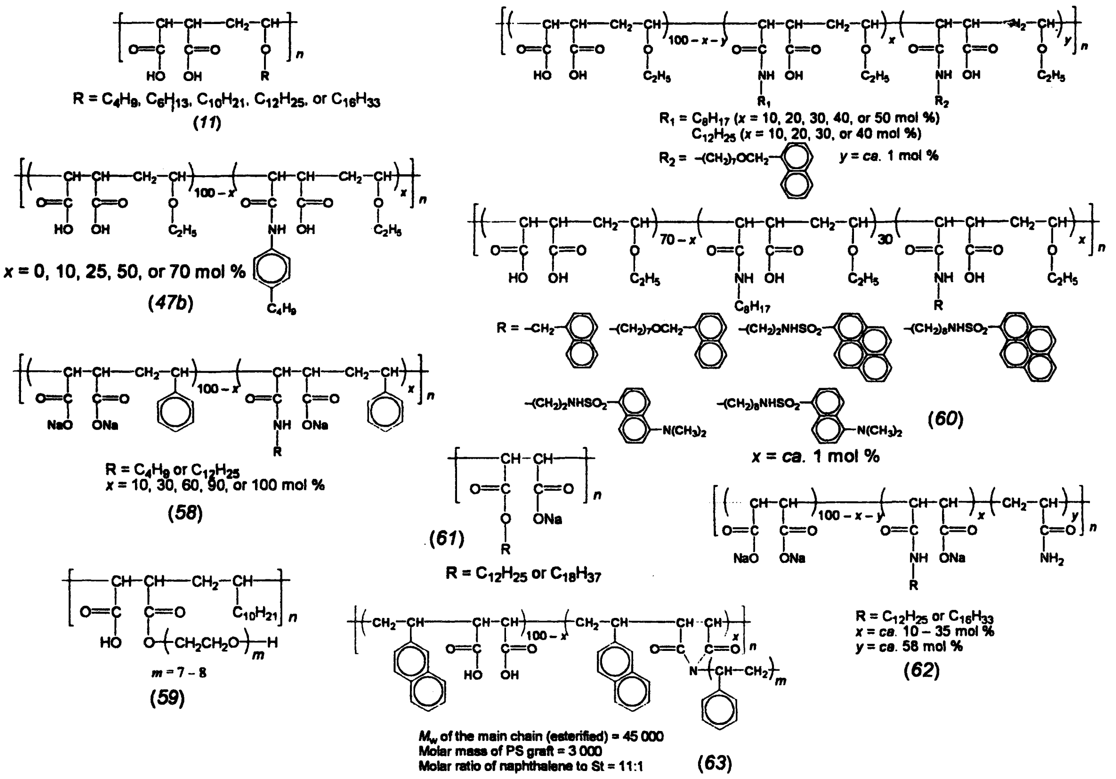
R = C_4H_9, C_6H_{13}, $C_{10}H_{21}$, $C_{12}H_{25}$, or $C_{16}H_{33}$
(11)
x = 0, 10, 25, 50, or 70 mol %
(47b)
R = C_4H_9 or $C_{12}H_{25}$
x = 10, 30, 60, 90, or 100 mol %
(58)
m = 7 - 8
(59)
R_1 = C_8H_{17} (x = 10, 20, 30, 40, or 50 mol %)
$C_{12}H_{25}$ (x = 10, 20, 30, or 40 mol %)
R_2 = $-(CH_2)_7OCH_2-$
y = ca. 1 mol %
R = $-CH_2-$ $-(CH_2)_7OCH_2-$ $-(CH_2)_2NHSO_2-$ $-(CH_2)_8NHSO_2-$ $-(CH_2)_2NHSO_2-$ $-(CH_2)_8NHSO_2-$
x = ca. 1 mol %
(60)
R = $C_{12}H_{25}$ or $C_{18}H_{37}$
(61)
R = $C_{12}H_{25}$ or $C_{16}H_{33}$
x = ca. 10 – 35 mol %
y = ca. 58 mol %
(62)
M_w of the main chain (esterified) = 45 000
Molar mass of PS graft = 3 000
Molar ratio of naphthalene to St = 11:1
(63)

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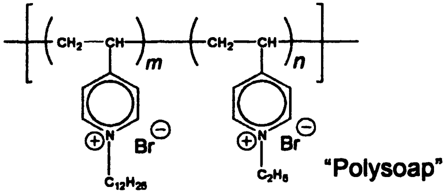
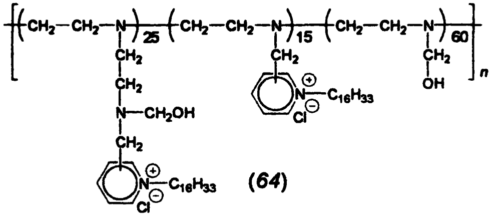
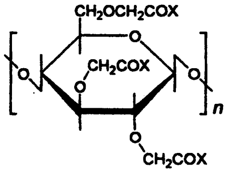
Chart 6. Amphiphilic Polyelectrolytes by Chemical Modification



(*12*)

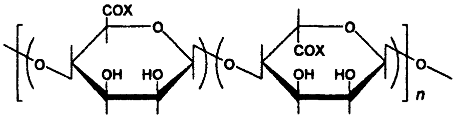


(*64*)



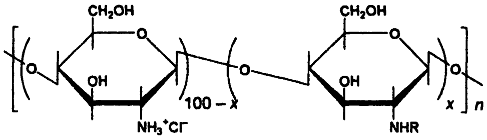
X = OH or $NHC_{12}H_{25}$ (1.2 mol %)

(*65*)



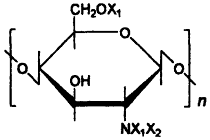
X = ONa (> 61 mol %), $OCH(CH_3)CH_2OH$, or $NHC_{12}H_{25}$ (9 mol %)

(*66*)



R = C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, or $C_{14}H_{29}$
x = 2 – 12 mol %

(*67*)



the degree of substitution:
CH2COONa (1.1)
COCH3 (0.85)
C12H25 (0.01 or 0.016)
C14H29 (0.03 or 0.044)

X1 = H or CH2COONa
X2 = H, COCH3, CH2COONa, or CnH2n+1 (n = 12 or 14)

(*68*)

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General Considerations of Hydrophobic Associations in Amphiphilic Polyelectrolytes

Hydrophobic associations in amphiphilic polyelectrolytes occur competing with electrostatic repulsions between ionic sites in the same polymer chain and/or different polymer chains. The balance of these opposing interactions is primarily a function of the numbers of hydrophobes and charges in a polymer chain as well as the size of the hydrophobe.

Hydrophobic Association in Block Amphiphilic Polyelectrolytes.

In aqueous solutions, **AB** and **ABA** block copolymers, where **A** and **B** represent hydrophilic and hydrophobic sequences, respectively, which contain only one hydrophobic block sequence in a polymer chain, often undergo micellization similar to small molecular surfactants (Figure 1). A typical micelle formed from an amphiphilic block polymer has a spherical dense core made of hydrophobic blocks and a corona (or shell) composed of ionic blocks swollen by a solvent. The micelle core in aqueous solution may be glassy or liquidlike, depending on the type of hydrophobic blocks. For example, block copolymers of polystyrene (PS) and poly(methacrylic acid) (PMAA) form spherical micelles in water with a glassy core of PS blocks and extended PMAA block chains forming a corona (*13*). However, PS-*block*-PMAA cannot be dissolved directly into water. In a dioxane/water (80/20, v/v) mixture, PS-*block*-PMAA forms equilibrium micelles. A stepwise dialysis of the dioxane/water solution of the PS-*block*-PMAA with a gradual increase in water content allows one to obtain eventually an optically clear aqueous solution of micelles which are referred to as "kinetically frozen micelles" (*13*). Block copolymers of PS and poly(acrylic acid) (PAA) form various types of nanostructures with well-defined morphologies such as a sphere, rod, and lamella in a mixture of *N*,*N*-dimethylformamide and water followed by stepwise dialysis (*14*).

In the case of **BAB** type block copolymers, unimers (single molecules) may exist as a loop or extended form in equilibrium. The looped unimers behave as if they were **AB** type diblock copolymers, forming a core-corona micelle with a corona of looped hydrophilic blocks, whereas the extended unimer may act as a linker between two micelles (Figure 1). Therefore, **BAB** type block copolymers would form a network structure, depending on the populations of the looped and extended unimers.

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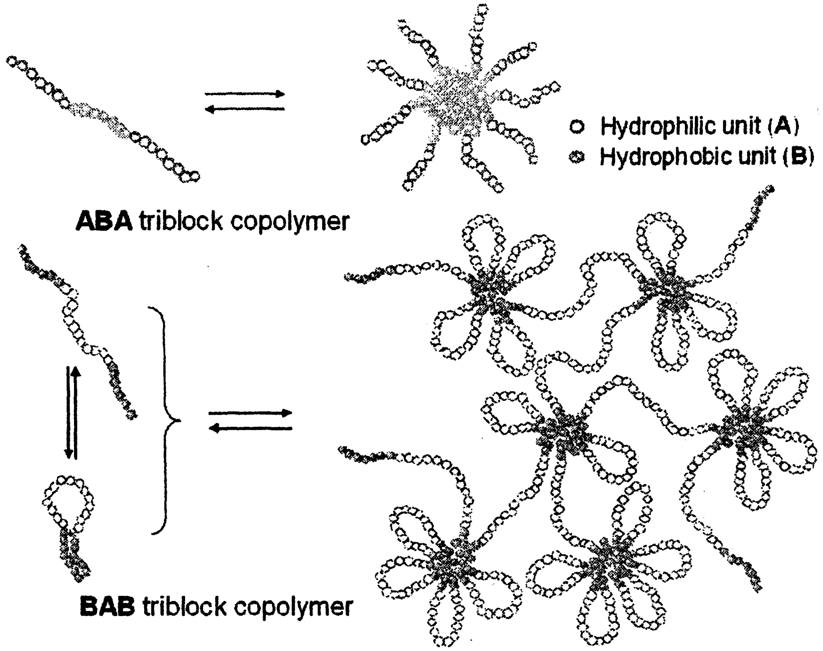
○ Hydrophilic unit (A)
● Hydrophobic unit (B)
ABA triblock copolymer
BAB triblock copolymer

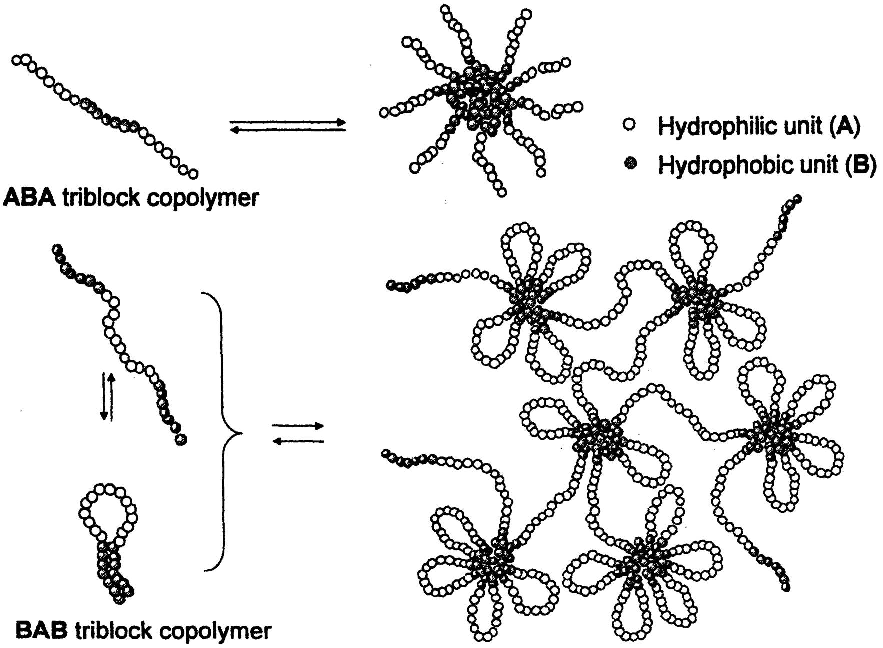
○ Hydrophilic unit (A)
● Hydrophobic unit (B)
ABA triblock copolymer
BAB triblock copolymer

Figure 1. Conceptual illustrations of hydrophobic association of amphiphilic ABA and BAB triblock copolymers.

Self-Association of Random Amphiphilic Polyelectrolytes.

Hydrophobic association in random copolymers occurs either in an inter- or intramolecular fashion, the former resulting in a crosslink and the latter in a loop (Figure 2). Nanostructures formed from amphiphilic random copolymers are greatly different depending on whether inter- or intramolecular hydrophobic association predominantly occurs. When hydrophobes undergo completely intermolecular association (Figure 3), polymer chains are crosslinked, leading to a large increase in solution viscosity. An infinite network may be formed, as the hydrophobe content is increased to a certain level, yielding gels. Figure 4 illustrates an extreme case where polymer-bound hydrophobes undergo completely intramolecular associations, yielding single-molecular or unimolecular micelles. When the content of a hydrophobe in a polymer is sufficiently low, a "flower-like" unimolecular micelle may be formed, which consists of a hydrophobic core surrounded by ionic loops as theoretically predicted (*15*). As the content of the hydrophobe in the polymer is increased, the flower-like micelle would become unstable because an icreasing portion of the hydrophobic core is exposed to water. This would lead to a further collapse into a more compact micelle with a third-order structure driven by secondary association of hydrophobic cores of the flower-like micelles (*16*). However, in most cases, intramolecular hydrophobic association occurs concurrently with intermolecular association, where intermolecularly bridged flower-like micelles may be formed. Intra- vs. intermolecular hydrophobic associations are a strong function of the hydrophobe content in the copolymer. There is a general tendency that intermolecular association is favorable when the hydrophobe content is very low and it becomes unfavorable with increasing the hydrophobe content (*17*).

Characterization Methods

The elucidation of association structures and their dynamic properties of amphiphilic polyelectrolytes in aqueous media by numerous analytical methods is now reasonably well established. Since different analytical techniques provide information on different length scales depending on the principle of the method, the use of different analytical methods in combination is particularly important. Most commonly employed are fluorescence (short range), light scattering (intermediate range), and rheometric techniques (long range). This section describes analytical methods employed for the characterization of self-association of random copolymers of NaAMPS and *N*-dodecylmethacrylamide (poly(NaAMPS/C$_n$MAm)) (Scheme 1) (*16*).

As schematically illustrated in Figure 5, poly(NaAMPS/C$_n$MAm), where 6 ≤

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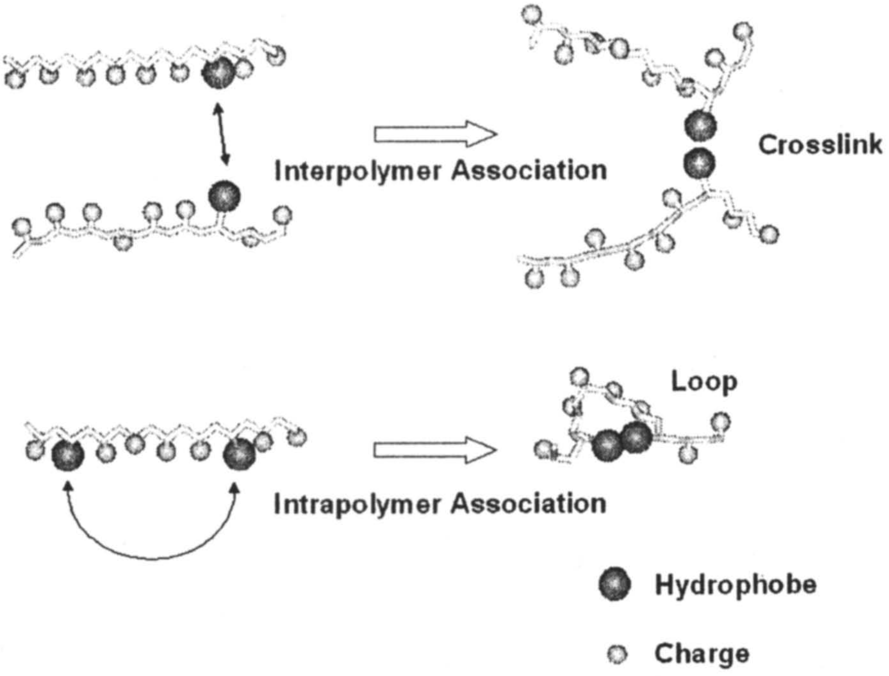
Interpolymer Association
Crosslink
Intrapolymer Association
Loop
Hydrophobe
Charge

Figure 2. Inter- and intrapolymer associations of hydrophobes.

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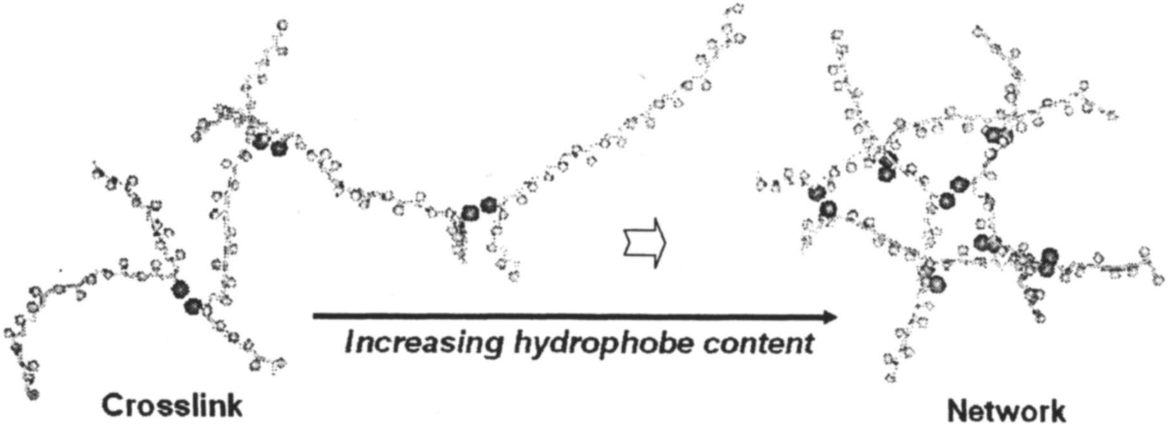
Increasing hydrophobe content
Crosslink
Network

Figure 3. Completely Interpolymer associations of hydrophobes forming crosslinks.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

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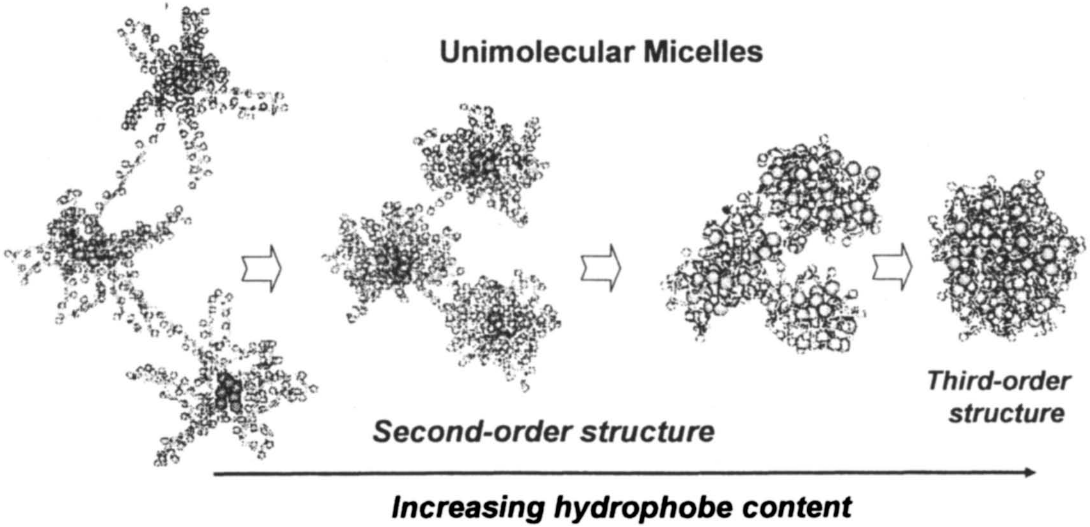
Unimolecular Micelles
Second-order structure
Third-order structure
Increasing hydrophobe content

Figure 4. Completely Intrapolymer associations of hydrophobes forming unimolecular micelles.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

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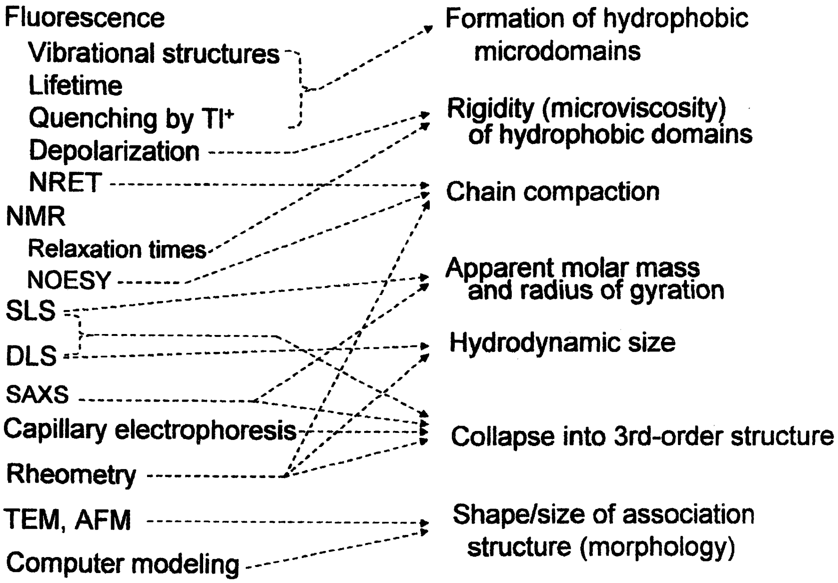
Scheme 1. Various Characterization Techniques with Different Length Scales


Fluorescence
Vibrational structures
Lifetime
Quenching by Tl⁺
Depolarization
NRET
NMR
Relaxation times
NOESY
SLS
DLS
SAXS
Capillary electrophoresis
Rheometry
TEM, AFM
Computer modeling
Formation of hydrophobic microdomains
Rigidity (microviscosity) of hydrophobic domains
Chain compaction
Apparent molar mass and radius of gyration
Hydrodynamic size
Collapse into 3rd-order structure
Shape/size of association structure (morphology)

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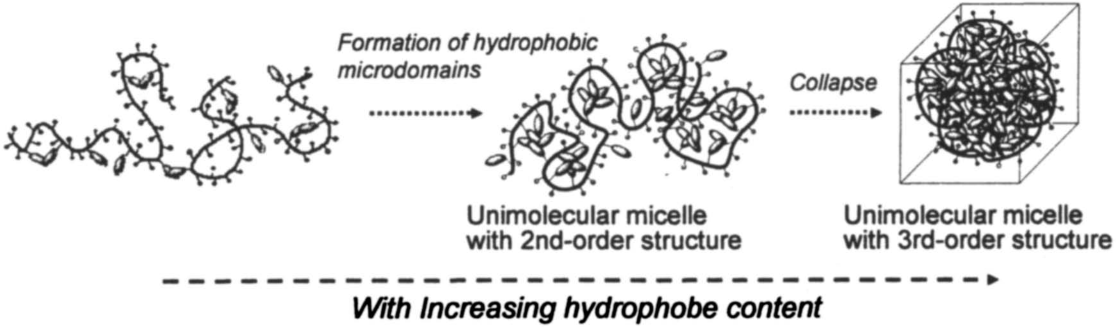
Formation of hydrophobic microdomains
Collapse
Unimolecular micelle with 2nd-order structure
Unimolecular micelle with 3rd-order structure
With Increasing hydrophobe content

Figure 5. Conceptual illustration of unimolecular micelles of second- and third-order structures formed from poly(NaAMPS/CnMAm) in water

$n \leq 18$, undergoes predominantly intramolecular self-association of C_n groups in aqueous media forming unimolecular micelles. However, when the C_nMAm contents are as low as 5 mol% in the case of $n = 12$, the polymer undergoes simultaneously inter- and intramolecular hydrophobic associations (*17d*). As the C_nMAm content is increased, unimolecular micelles with a second-order structure are first formed, which is followed by a collapse into a third-order structure as the C_nMAm content is further increased.

Methods with Short Dimensional Range.

Fluorescence Spectroscopy

(1) Steady-State Fluorescence Spectra. The formation of hydrophobic microdomains can be most conveniently detected by measuring fluorescence spectra of a fluorescence probe that is solubilized in aqueous solutions of an amphiphilic polyelectrolyte. The probe should be hydrophobic or amphiphilic in nature so that it can be incorporated into hydrophobic microdomains. Polymers can be labeled with a relatively small amount of fluorescent chromophores, such as pyrene and naphthalene, by copolymerization with a choromophore-bearing polymerizable monomer. The wavelength and/or the intensity of fluorescence emission maxima of some fluorophores are sensitive to the micropolarity around the fluorophore. Pyrene is most often used as a fluorescent probe or label on the basis of the fact that the ratio of the intensities of the third and first vibronic peaks in the fluorescence spectrum (I_3/I_1) is sensitive to the polarity of microenvironments, i.e., I_3/I_1 is larger in less polar media in which pyrene is solubilized (*18*).

(2) Fluorescence Lifetime. Fluorescence lifetime measurements also provides information about the formation of hydrophobic microdomains due to the fact that fluorescence lifetimes of aromatic molecules become longer in less polar median. Thus, a prolonged lifetime observed with an aromatic probe or label is an indication of the formation of hydrophobic microdomains (*16*).

(3) Fluorescence Quenching. The presence of hydrophobic microdomains can be confirmed by fluorescence quenching of aromatic chromophores labeled on an amphiphilic polyelectrolyte with use of a water-soluble quencher such as thallium ions (Tl^+) and nitromethane. When the fluorescence labels are incorporated into hydrophobic microdomains, the labels are protected from the access of the quencher, and hence fluorescence quenching is suppressed. The extent of the suppression of the quenching reflects the extent of the formation of hydrophobic microdomains (*16a*). However, one should be careful about nitromethane because this quencher may be partitioned into hydrophobic microdomains to some extent whereas the quenching by Tl^+ ions is strictly confined to the aqueous phase.

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(4) Fluorescence depolarization. Fluorescence depolarization techniques provide information about rigidity or microviscosity of hydrophobic microdomains in which labels are incorporated. When light polarized parallel to the transition moment passes through a chromophore, the chromophore may be excited to a singlet state, emitting polarized fluorescence. If rotational motion of the chromophore is slow enough compared to its fluorescence lifetime, the polarized fluorescence can be observed. On the other hand, if the rotational motion is fast enough, depolarized fluorescence will be observed. From fluorescence anisotropy (r) calculated on the basis of polarized steady-state fluorescence intensities, one can calculate rotational correlation time (τ_ϕ) for the label. If one observes a prolonged τ_ϕ value, then one can qualitatively relate the increased τ_ϕ value to an increased microviscosity of hydrophobic microdomains where the fluorophore exists.

(5) Nonradiative Energy Transfer (NRET). NRET between an energy donor and energy acceptor covalently attached to a polymer chain provides a sensitive tool to detect conformational changes (*16a,19-21*). The efficiency of NRET from a donor to an acceptor depends on their separation distance (R), their orientation, and the refractive index of media. The energy transfer efficiency (E) depends strongly on R according to $E = R_0^6/(R_0^6 + R^6)$ where R_0 is the Förster radius, at which E is 0.5 for rotationally averaged pairs. Thus, an increase in E indicates an increase in the fraction of donor-acceptor pairs which come close to each other within the distance of R_0. When a donor and an acceptor are covalently attached to the same polymer chain, the efficiency of NRET strongly reflects the conformational dimension of the polymer chain. On the other hand, in mixed solutions of polymers carrying either only a donor or an acceptor, the efficiency of NRET between the two labels corresponds to the extent of intermolecular association.

Nuclear Magnetic Resonance (NMR)

(1) Relaxation Times. NMR relaxations are strongly dependent on the mobility of the measured nuclei. Thus, spin-lattice and spin-spin relaxation times provide information about the mobility of hydrophobes in an association structure in solution (*16a,22*).

(2) Nuclear Overhauser Effect (NOE). When nuclei are located in proximity (normally, < *ca.* 5 Å), NOE can be observed arising from dipole-dipole interactions between the nuclei. Since the intensity of NOE is inversely proportional to the sixth power of the distance between the nuclei, a detailed analysis of an NOE spectrum may yield information about the spatial structure of macromolecules in solution, thus NOE spectroscopy (NOESY) providing a useful tool to study conformational changes of polymer chains (*23*).

Methods with Intermediate Dimensional Range

Static Light Scattering (SLS) and Dynamic Light Scattering (DLS)

SLS has been used widely to measure an apparent molar mass (M_w) and radius of gyration (R_g) of polymer micelles in solution. Light is scattered due to a difference in refractive index between a solute (scatterer) and a solvent. In SLS measurements, the Rayleigh ratio, R_θ, defined as $R_\theta \equiv Ir^2/I_0$, is usually measured. Here, I_0 is the intensity of the incident light, and I is the scattered intensity per unit scattering volume at a distance r from the scattering volume. By measuring R_θ with varying concentrations of a scatterer and scattering angles, M_w and R_g can be determined

DLS (photon correlation spectroscopy (PCS)) can also be applied to obtain the hydrodynamic radius of the micelle. By measuring the intensity fluctuation of scattered light by the micelles (which undergo Brownian diffusion), one can obtain the diffusion coefficient of the micelles from which the hydrodynamic radius can be calculated by using the Stokes-Einstein equation.

Small Angle X-ray Scattering (SAXS) and Small Angle Neutron Scattering (SANS)

Micelle size and shape of block and graft copolymers can be determined by SAXS or SANS. Since the scattering vector of X-ray or neutron beam is longer than that of visible light, structures of smaller scale (e.g., the core size in micelle-like aggregates) can be examined using small angle X-ray or neutron scattering.

Capillary Electrophoresis (CE)

The collapse of a second-order structure into a third-order structure can be detected by capillary electrophoresis. Figure 6 shows an example for poly(NaAMPS/C_{12}MAm) with varying C_{12} contents. The electropherogram suddenly becomes significantly narrower at a C_{12} content of 40 mol%. This is an indication that the second-order structure collapses into a third-order structure. The unimolecular micelle with a third-order structure is a rigid globule with a narrow distribution in size, which is also indicated by SAXS and SLS data (*16a, 24,*).

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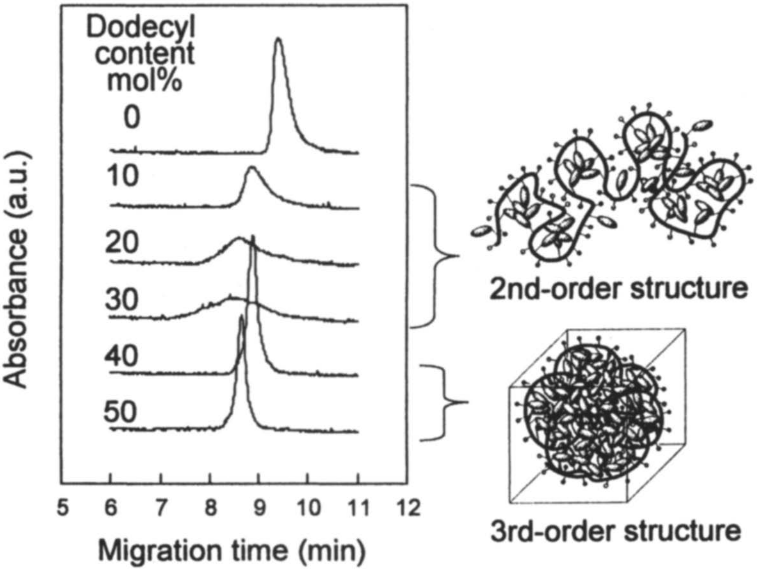

Figure 6. Electropherograms for poly(NaAMPS/C_{12}Mam) with varying hydrophobe contents in water at pH 9.

Morphology

(1) Transmission Electron Microscopy (TEM). For polymer micelles, TEM measurements are usually carried out with a negative staining or freeze-fracture technique or under cryogenic conditions (cryo-TEM) because organic molecules are easily damaged by electron beam.

(2) Scanning Probe Microscopy (SPM). Advantages of SPM are that (i) a high resolution can be obtained in the atomic scale and (ii) SPM is possible for interfaces between solid and vapor phases or solid and liquid phases.

In scanning tunneling microscopy (STM), tunneling current between a metal probe and sample surface is monitored during the scan, and, in atomic force microscopy (AFM), atomic force between a probe and surface is monitored during the scan. STM is applicable only to surfaces of conductive materials, but AMF is also useful for surfaces of insulators (*25*).

Figures 7a and b represent examples of TEM and AFM images for unimolecular micelles with a third-order structure formed from poly(NaAMPS/C_{12}MAm) with a 50 mol% C_{12} content. Molecular models for the unimolecular micelle are compared in Figures 7c and d. To obtain the molecular model, the energy minimization and molecular dynamics calculation were performed with Discover 3 (MSI). It can be easily seen from the models how the polymer main chain is folded into a highly compact conformation.

Methods with Long Dimensional Range

Rheometry

In rheometry, a well-defined shear stress is applied to a sample solution, and a viscoelastic response is observed. Applying a steady-shear stress to a sample solution provides steady-shear viscosity, an important property of associative amphiphilic polymers. Through measurements of steady-shear viscosity at varying shear rates, shear thickening or shear thinning may be observed. Shear thickening and shear thinning are phenomena where steady-shear viscosity increases and decreases with increasing shear rate, respectively. Zero-shear viscosity, a steady-shear viscosity at zero-shear rate, is often used to describe a solution property of an associative amphiphilic polyelectrolyte. Storage and loss moduli (G' and G'', respectively) can be obtained, by applying an oscillatory-shear stress, as a function of angular frequency. If a single-element Maxwell model is assumed, a plateau modulus (G_0) and a terminal relaxation time (λ) may be obtained. According to a simple theory for transient networks or reversible physical bonds in which network junctions can breakup and recombine, the magnitude of G' at a high frequency is related to the number

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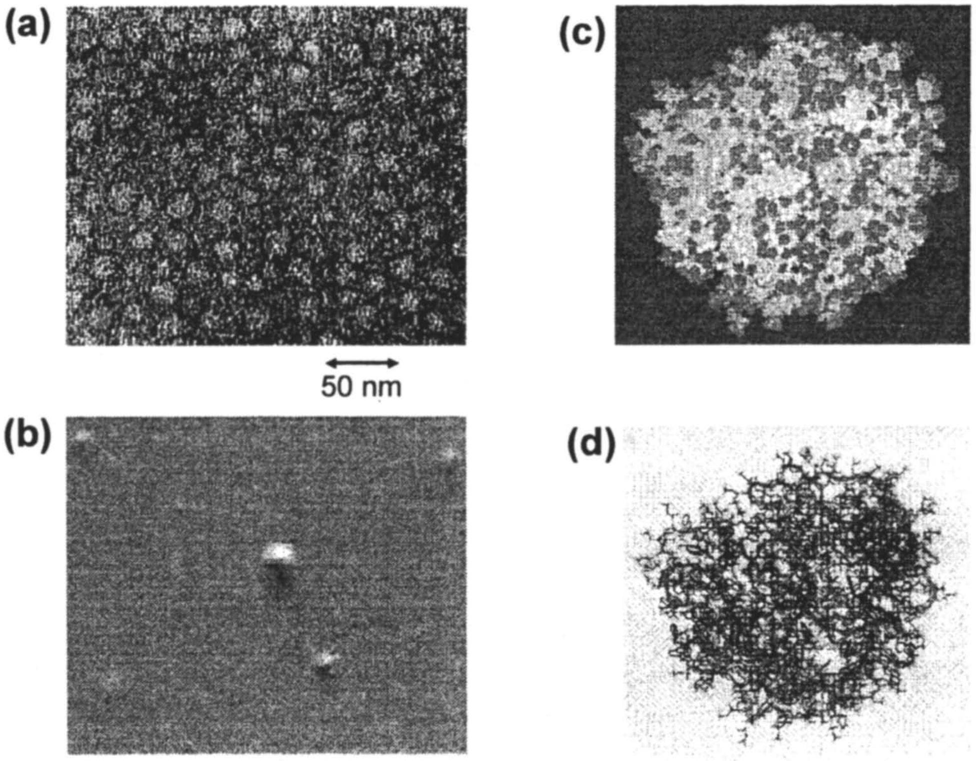

Figure 7. (a) TEM and (b) AFM images and (c) space filling and (d) stick and ball models for unimolecular micelles of a third-order structure.

density of mechanically active chains. The value of λ, roughly estimated from a crossover frequency at which *G*' and *G*" intersect, is a rough measure of a rheological terminal relaxation time that is associated with the relaxation time of a mechanically active chain.

Viscoelastic properties of associative amphiphilic polyelectrolytes can be also investigated by a technique of superposition of oscillations on steady-shear flows (*26*). An advantage of this technique is that, with increasing shear rate of the steady-shear, *G*' and *G*" at low angular frequencies of flexible polymer systems are greatly reduced, allowing one to observe the long time scale end of the relaxation spectrum (i.e., plots of *G*' vs ω and *G*" vs ω) for sample solutions with a longer terminal relaxation time.

Concluding Remarks

Extensive studies of amphiphilic polyelectrolytes by a large number of research groups have yielded a good deal of progress in the understanding of underlying structure-property relationships. A practically important property of amphiphilic polyelectrolytes is their ability to solubilize hydrophobic substances that are otherwise only sparingly soluble in water. Molecular design of amphiphilic block polyelectrolytes is expected to provide specified solubilization performances for the development of environmentally benign aqueous systems. The importance of amphiphilic random polyelectrolytes will further increase because these polymers will provide excellent models for the understanding of the behavior of more complicated biological polymers, given all the important biological macromolecules are random polyelectrolytes with amphiphilic nature. The manipulation of spatial structures formed from self-associations of amphiphilic polyelectrolytes in aqueous media will continue to be an area of great scientific and technological interest.

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Chapter 3

Synthetic Polyzwitterions: Water-Soluble Copolymers and Terpolymers

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Structural features of polyzwitterionic co- and terpolymers and their resulting solution behavior can be tailored by proper monomer selection and choice of synthetic pathway. In this chapter, we review the structures and solution behavior of major polyampholytes and polybetaines prepared in our research group and by others. Here, we concentrate on acrylamido-based systems due to their pervasive use in applications where hydrolytic resistance is important. The electrolyte tolerance and solubility of water-soluble polyampholytes and the pH-responsiveness of amphoteric polyzwitterions are attributes of potential commercial utility in pharmaceutical, personal care, mining, and oil field chemical formulations.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

Introduction

Ion-containing polymers are an important class of water-soluble polymers utilized in many applications including enhanced oil recovery (EOR), drag reduction, water treatment, papermaking, mining, and formulation of personal care items and pharmaceuticals *(1-2)*. A variety of ionic co- and terpolymers of the industrially important monomer acrylamide have been prepared utilizing anionic, cationic, or zwitterionic co-monomers. Such systems are routinely synthesized *via* conventional free radical copolymerization directly in aqueous media or by heterogeneous micellar inverse emulsion, or inverse microemulsion techniques *(3)*. Recently, controlled polymerization techniques including reversible addition chain-transfer polymerization (RAFT) have been used to prepare block copolymer polyelectrolytes and polybetaines *(4-5)*. Water-soluble, RAFT- based block copolymers are reviewed in detail in Chapter 6 of this book.

In order to understand the often unique behavior of ion-containing polymers in aqueous media, it is important to examine general structure features of the two major classes. Polyelectrolytes contain *either* anionic or cationic charges along the polymer chain, while polyampholytes contain *both* anionic and cationic moieties *(1,6-7)*. The aqueous solution properties (i.e. intrinsic viscosity, hydrodynamic volume, etc.) of polyelectrolytes and polyampholytes are profoundly different and are dictated primarily by the intra- and intermolecular electrostatic interactions that occur among the charged groups in aqueous media *(8-13)*. In dilute, salt-free aqueous solutions, coulombic repulsion between like charges along the polyelectrolyte chain leads to an expansion in the hydrodynamic volume of the polyelectrolyte coil; however, addition of small molecule electrolytes (e.g. NaCl) results in coulombic shielding and a decrease in hydrodynamic volume and thus solution viscosity. This solution behavior illustrated in Figure 1 is the well-known the *polyelectrolyte effect.*

By contrast, coulombic interactions between positively and negatively charged repeat units of polyampholytes reduce hydrodynamic volume, and the polymer adopts a collapsed or globular conformation in dilute, salt-free aqueous media *(6,13)*. In some instances, the electrostatic interactions are so strong that the polymer may become insoluble. Upon addition of simple electrolytes (i.e. NaCl) to a polyampholyte solution in the dilute regime, an increase in hydrodynamic volume of the polymer coil is observed due to the screening of the intramolecular charge-charge attractions, allowing the transition from a globule to a random coil conformation. Such solution behavior is known as the *anti-polyelectrolyte effect* and is evidenced by increased polymer hydrodynamic volume and solution viscosity (shown in Figure 2).

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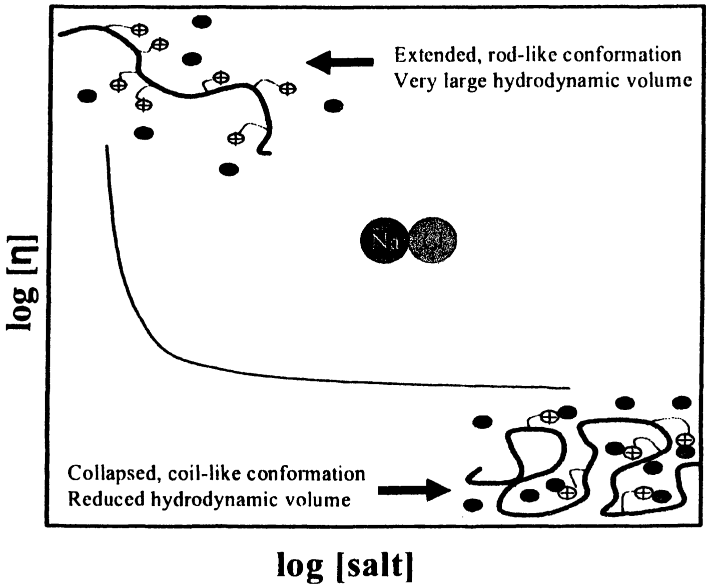
Extended, rod-like conformation
Very large hydrodynamic volume
Na
log [n]
Collapsed, coil-like conformation
Reduced hydrodynamic volume
log [salt]

Figure 1. The effect of salt addition on the intrinsic viscosity ([η]) of a polyelectrolyte in aqueous solution.

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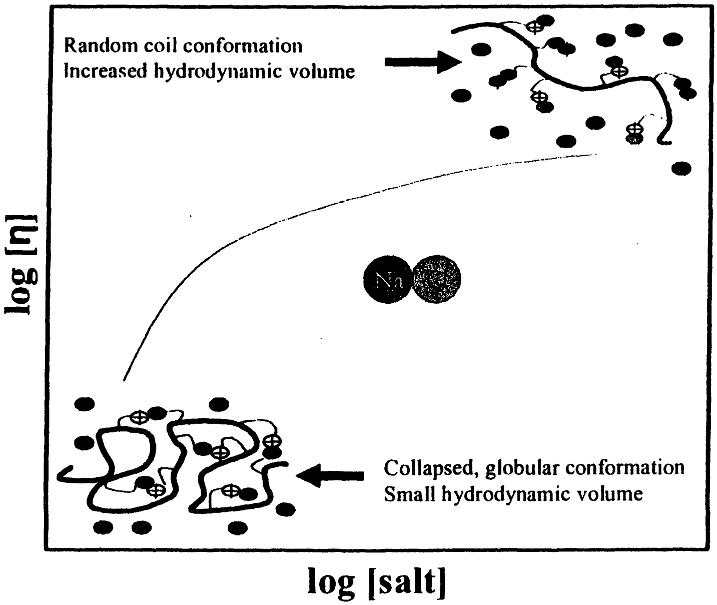
Random coil conformation
Increased hydrodynamic volume
Na
Collapsed, globular conformation
Small hydrodynamic volume
log [η]
log [salt]

Figure 2. The effect of salt addition on the intrinsic viscosity ([η]) of a polyampholyte in aqueous solution.

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In addition to interactions with small molecule electrolytes, other factors such as charge density and distribution, charge balance, monomer sequence distribution (random, alternating, and block), and the nature of the ionizable groups along the macromolecular backbone play key roles in governing macromolecular conformational properties and rheological behavior of polyzwitterions in aqueous solution. For polyampholytes, the magnitude of the globule-to-coil transition, the extent of polymer solubility, and the hydrodynamic volume are typically governed by the charge density of the system *(13)*. Larger concentrations of electrolytes are needed to elicit coil expansion as charge density is increased; however, the magnitude of hydrodynamic volume increase observed is greater with an increased number of zwitterionic interactions. Imbalanced polyampholytes (i.e. polyampholytes with a net charge) exhibit more complex behavior that is dependent on the degree of charge imbalance, often referred to as charge asymmetry *(12-14)*.

The effects of charge density and charge distribution along the polyampholyte chain, as well as the extent of charge asymmetry, on chain conformation have been the subject of continued research. Charge density is typically defined as the total number of anionic and cationic groups incorporated into a given polymer, and charge asymmetry is representative of the degree of charge imbalance (i.e "net" charge) present on the polyampholyte chain *(6)*. Equation 1 is used to calculate the charge asymmetry, σN, of a given polyampholyte. For a polyampholyte consisting of N repeat units containing a fraction of positive repeat units, f_+, and a fraction of negative repeat units, f_-, the σN is defined where $N_+ = f_+ \cdot N$ is the number of positive (cationic) repeat units and $N_- = f_- \cdot N$ is the number of negative (anionic) repeat units present in the ampholytic terpolymer.

$$\sigma N = \frac{(N_+ - N_-)^2}{N_+ + N_-} \qquad (1)$$

Polyampholytes that have unbalanced charge ratios (i.e. possess a net charge) and higher charge asymmetries exhibit both polyampholyte and polyelectrolyte behavior, depending on the degree of charge imbalance. As the degree of charge imbalance on a polyampholyte chain increases, the polymer tends to behave in a manner that is more charactertistic of a conventional polyelectrolyte. Figure 3 depicts transitions that are experienced by a randomly incorporated polyampholyte chain with increasing charge asymmetry in dilute, salt-free, aqueous conditions as theorized by current models and Monte Carlo simulations *(6)*. Typically, polymers that have random incorporation of charged species exhibit more profound antipolyelectrolyte behavior than polyampholytes with alternating incorporations of the anionic and cationic moieties. This is due to long-range electrostatic interactions in the random species versus the alternating ones in which the interactions occur over short-ranges.

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The chemical nature of the charged groups on the polyampholyte is also critical to the solution properties. Polyampholytes bearing strong acids or salt-like functionalities such as sulfonic acids and quaternary ammonium derivatives, respectively, are generally insensitive to changes in solution pH; thus the charge balance and charge density is determined solely by the relative incorporations of the anionic and cationic monomers. However, in polyampholytes containing weak acid/base functionalities such as carboxylic acid and/or 1°, 2°, or 3° amine species, the charge density and charge balance of the polymer are determined by the relative incorporations of the ionizable monomers, the pK_a of the amphoteric species, and the solution pH. With this in mind, it is possible to produce terpolymers that exhibit triggerable polyampholyte behavior in response to changes in solution pH *(4,6)*. An example is that of a polyampholyte containing equimolar amounts of carboxylic acid and quaternary ammonium functional groups. At low pH, this polymer behaves as a cationic polyelectrolyte due to an overall net charge that is a result of virtually no ionization of the acidic groups. As the solution pH is raised, these groups are ionized, eventually establishing a charge balance, at which point the polymer exhibits polyampholyte behavior. For polyampholytes in which the amphoteric repeating units (for example carboxylic acid monomers) are present in excess of permanently charged mers, polyampholyte behavior is observed at the isoelectric point (IEP), the pH at which the number of cationic and anionic groups is equal. As the solution pH is adjusted from the IEP, polyelectrolyte behavior is observed due to the increase in the net charge.

Figure 4 provides experimental evidence of such a system. A random, charge-balanced terpolymer of AM, N-acryloyl valine, and (3-acrylamidopropyl)trimethyl ammonium chloride (APTAC) was synthesized in aqueous media and studied in the dilute regime for response to changes to solution pH and electrolyte concentration. The effects of charge asymmetry as well as the amphoteric nature of the carboxylate functionality determine the terpolymer's solution behavior, particularly in salt-free media. At low pH, high charge asymmetry results in polyelectrolyte behavior as evidenced by high solution viscosities. As the pH is raised, an IEP is reached and the charge asymmetry has its lowest value. A dramatic reduction in solution viscosity is observed due to chain collapse from an extended conformation to a more globular conformation characteristic of random, charge-balanced polyampholytes.

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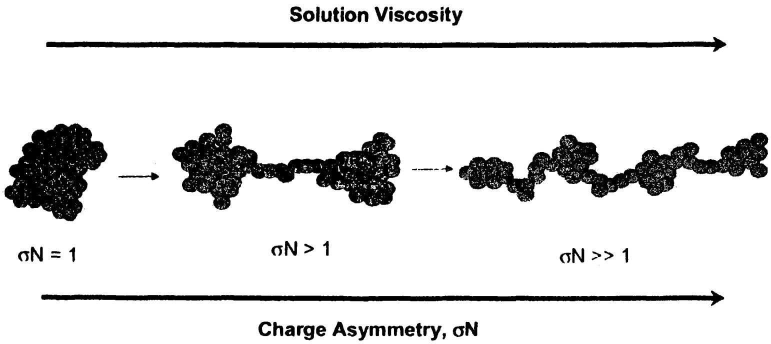

Figure 3. Transitions in the structure of a polyampholyte chain as a function of charge asymmetry (σN)

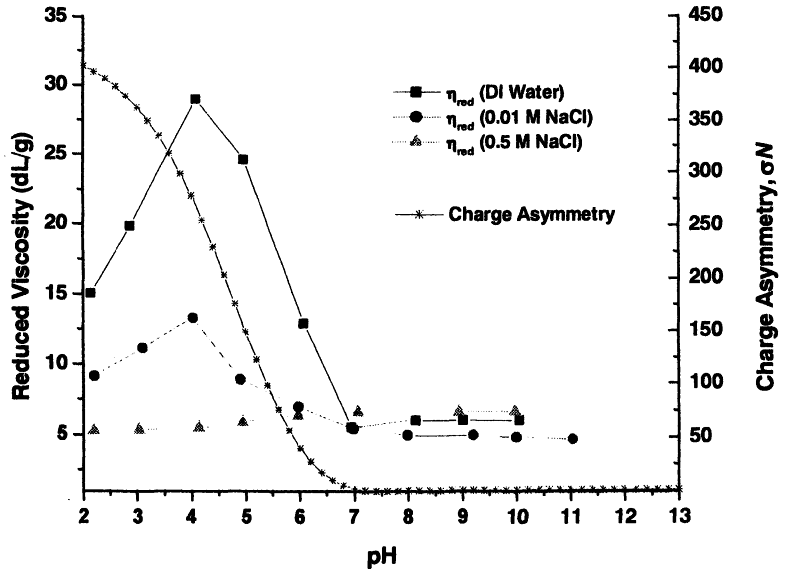

Figure 4. Charge asymmetry and reduced viscosity as a function of pH for a charge-balanced terpolymer in DI water, 0.01 M NaCl, and 0.5 M NaCl. Polymer concentration was 0.1 g/dL.

Model Water-Soluble PAM-Based Polyzwitterions

Extensive academic and industrial research has been directed toward the development of synthetic polyzwitterions based on polyacrylamide (PAM) due to potential industrial applications *(7,11)*. An important observation is that low charge density polyampholytes derived from the terpolymerization of cationic and anionic monomers with acrylamide (AM) typically have greater solubility and greater viscosifying ability than do high charge density polyampholyte copolymers *(15-19)*. Peiffer and Lundberg *(20-22)* reported early studies of low charge density polyampholytes and showed that these polyampholyte systems were more efficient viscosifiers by demonstrating the onset of intermolecular electrostatic associations at low polymer concentrations.

Most PAM-based polyampholytes reported in the literature are composed of AM, a sulfonated anionic monomer (e.g. sodium 2-acrylamido-2-methylpropanesulfonate, NaAMPS; 1, or sodium styrenesulfonate, NaSS; 2), and a quaternary ammonium cationic monomer (e.g. (2-acrylamido-2-methylpropyl)trimethylammonium chloride, AMPTAC; 3, (2-methacryloyloxyethyl)trimethylammonium chloride, MOETAC; 4 or (3-methacrylamidopropyl)trimethylammonium chloride, MAPTAC; 5) *(7,21,23-28)*. Figure 5 provides some examples of ionic monomers employed in the study of various polyampholyte systems.

Perhaps the two most important attributes of water-soluble polyzwitterions synthesized to date have been a) the electrolyte tolerance (maintenance of viscosity) of balanced polyampholytes desired in commercial formulations and b) the reversible viscosity behavior (pH responsiveness) of amphoteric polyampholytes. These attributes are clearly useful in pharmaceutical, agricultural, and personal care formulations, super-absorbency, enhanced oil recovery, mining, water remediation, and fracturing applications, to name a few. However, virtually all of the systems exhibit some degree of compositional drift during synthesis due to the reactivity differences of the (meth)acrylamido, methacrylic, and/or styrenic monomers. The resulting microstructures are often heterogeneous. Fortunately, the effects of compositional drift can be minimized when PAM-based polyampholytes are prepared using only acrylamido monomers *(16,25,29-30)*.

Polyampholyte terpolymers of AM, 1, and 3 were reported by our group *(25)*. These low charge density polyampholytes were prepared *via* free radical polymerization in 0.5 M NaCl yielding products with homogeneous compositions and random distributions of charged monomers. All charge balanced terpolymers exhibited polyampholyte behavior in the dilute solution regime, while solutions of imbalanced terpolymers exhibited polyelectrolyte characteristics.

The number of amphoteric, PAM-based polyampholytes published in the literature is relatively small. Amphoteric monomers (2-acrylamido-2-

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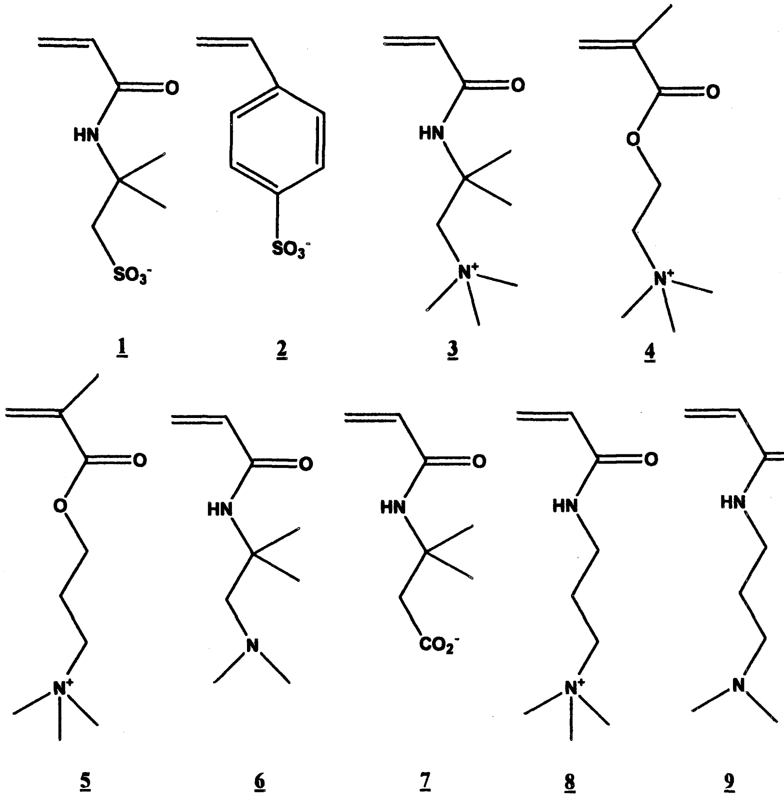
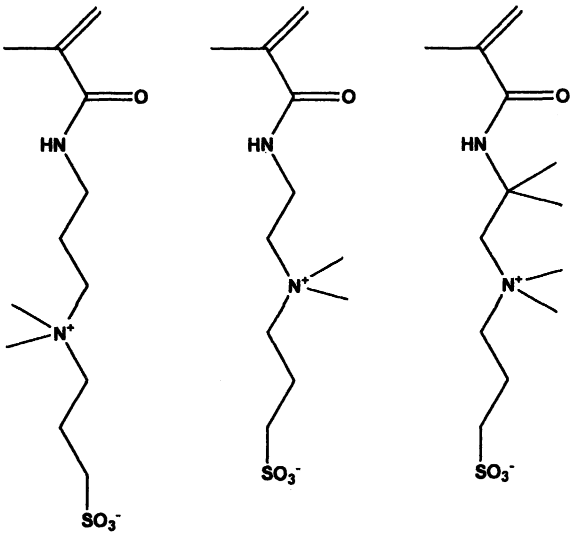


Figure 5. Examples of anionic and cationic monomers employed in polyampholyte synthesis.

methylpropyl)dimethyl-ammonium chloride (AMPDAC); 6) or sodium 3-acrylamido-3-methylbutanoate (NaAMB; 7) have been polymerized with 1, 3, or 8 (Figure 5), respectively *(1,16,29,31-33)*. In these systems, only one of the ionic monomers in the polyampholytes is pH-responsive. Preparation of PAM-based polyampholytes containing pH-responsive cationic *and* anionic groups (e.g. 6 and 7) resulted in formation of highly swollen gels. The formation of these gel networks is attributed to the presence of inter- and/or intra-chain interactions between the carboxylate and tertiary ammonium groups which could not be disrupted by electrolyte addition or adjustments in solution pH *(34)*.

PAM-based polybetaine copolymers have received significantly less attention as compared to their polyampholyte counterparts (See also Chapter 4 in this book). Such polybetaines typically contain non-pH-responsive sulfobetaine comonomers (Figure 6), such as 3-[(3-methacrylamidopropyl)dimethyl-ammonio]-propanesulfonate (MAPDAPS); 10), 3-[(methacryloxyethyl) dimethylammonio]-propanesulfonate (MOEDAPS); 11), or 3-[(2-acrylamid-2-

methylpropyl)dimethylammonio]-propanesulfonate (AMPDAPS; 12). Quaternization of tertiary amine-containing vinyl monomers with 1,3-propanesultone provides the synthetic pathway for betaine monomer production *(35)*. Salazar in our group *(36)* and Schulz and coworkers *(37)* have reported PAM-based sulfobetaine copolymers as drag reducing agents and viscosifiers for use in brine solutions.



10 11 12

Figure 6. Zwitterionic sulfobetaine monomers employed in the synthesis of non-pH-repsonsive polybetaine copolymers with AM.

In addition to the non-pH-responsive sulfobetaine monomers, copolymers of AM with various acrylamido carboxybetaine comonomers that vary by the number of methylene spacer units between the quaternary ammonium and carboxylate groups have also been examined (38-41). These monomers, shown in Figure 7, include 2-(2-acrylamido-2-methylpropyldimethylammonio)ethanoate (AMPDAE; 13), 4-(2-acrylamido-2-methylpropyldimethylammonio)butanoate (AMPDAB; 14), 4-(2-acrylamido-2-methylpropyldimethylammonio)hexanoate (AMPDAH; 15), and 3-[(3-acrylamidopropyl)dimethylammonio]propionate (AMDAP; 16). Copolymers of AM with 14 exhibited the most pronounced salt and pH-responsiveness. The transition from polyzwitterion to polyelectrolyte at low pH resulted in dramatic increases in solution viscosity due to the increased hydrodynamic volume. Extending the length of the alkyl chain separating the charged moieties rendered the carboxybetaine more hydrophobic thus reducing the solubility of the copolymers in aqueous environments.

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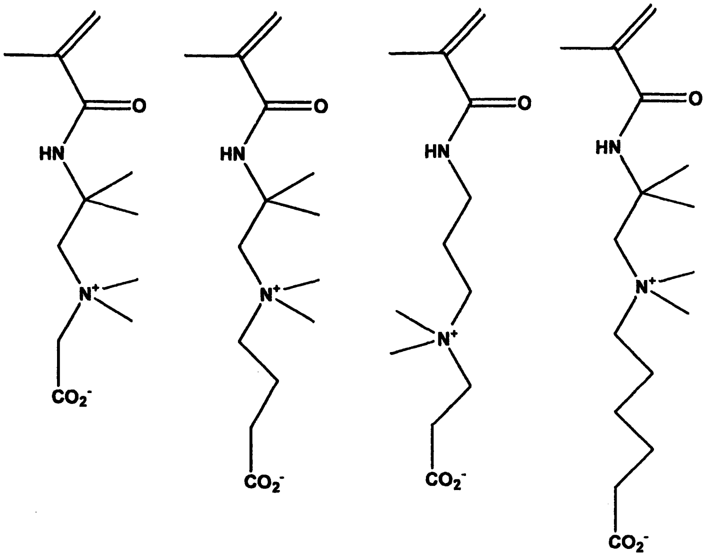

13 14 15 16

Figure 7. Zwitterionic carboxybetaine monomers employed in the synthesis of pH-responsive polybetaine copolymers with AM.

Other areas of academic and industrial endeavor have included the synthesis of hydrophobically modified (HM) water-soluble polymers by micellar copolymerization and the study of the resulting solution behavior in aqueous media. These hydrophilic copolymers contain small amounts (typically ≤ 1 mol %) of hydrophobic comonomers that promote viscosification through intermolecular hydrophobic associations *(42–47)*. Often referred to as associative thickeners (ATs), the HM copolymers exhibit greater thickening efficiencies and more complex rheological properties as compared to those of their unmodified counterparts. Several polymer systems investigated by our group have proven to be effective ATs with pH- and shear-responsive behavior *(48-54)*. These systems have potential for application in areas including enhanced oil recovery, drag reduction, and in the formulation of coatings, personal care products, and cosmetics. Chapter 2 of this book overviews recent advances in the study of HM polyelectrolytes. The reader is also directed to reference *(55)* in the bibliography for a comprehensive review of this subject.

Efforts have been made to produce associative polyzwitterions (PZs) that combine the benefits of PZ salt tolerance and HM copolymer thickening efficiency. Salamone and coworkers *(56-63)* investigated unique HM polyampholytes that incorporated 2-methacryloyloxyethyl-*N*-alkyl-*N*,*N*-

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dimethylammonium bromide monomers that are cationic and hydrophobic in nature. In one study *(62)*, HM cationic monomers bearing alkyl chains of different lengths were used to prepare ion-pair comonomers (IPCs) with **1**. The resulting IPCs were copolymerized with AM to yield HM polyampholytes; subsequent rheological studies revealed that the solution viscosities of the terpolymers were dependent on the level of IPC incorporation and on the length of the alkyl chains *(61)*. As a result of the hydrophobic modification, these polyampholytes were shown to maintain solution viscosity over wide ranges of salt concentration. Candau and coworkers *(64)* reported the micellar copolymerization of AM, **1**, MOETAC, and either *N,N*dihexylacrylamide or *N*-ethylphenylacrylamide as the hydrophobic comonomer. The resulting HM polyampholytes exhibited both salt- and shear-responsive rheological behavior. Winnik and Wiyazawa *(65-66)* prepared phosphorylcholine-based HM polybetaines by postpolymerization modification of HM poly(*N*-isopropylacrylamide) with pendant amine moieties, and the solution behavior of the HM polybetaines was examined in mixed aqueous–organic media. Due to high levels of phosphobetaine and hydrophobic comonomer incorporation and the random sequence of comonomer incorporation, the polymers tended to behave as polymeric micelles and were not examined as ATs.

Acrylamide-based, HM polybetaines containing *N*-butylphenylacrylamide (BPAM) and varying amounts of the sulfobetaine monomer **10** or the carboxybetaine monomer **12** were synthesized by our group *via* micellar copolymerization *(67-69)*. The interaction of the hydrophobically modified (HM) polybetaines with selected small molecule surfactants in aqueous solution was investigated using rheological and surface tension analyses. The low charge density terpolymers exhibited greater viscosity enhancement with the addition of surfactant as compared to the high charge density terpolymers. The proposed mechanism for this behavior is shown in Figure 8.

The increase in viscosity with electrolyte addition to the HM polymer solutions is due to the bridging of polymer chains as a result of comicellization between polymer and surfactant. Pathway 1 (Figure 8) shows the formation of mixed micelles or hemimicelles. These hemimicelles are composed of the hydrophobes bound to the polymer chain comicellized with surfactant molecules. If hyrophobes from multiple polymer chains participate in the same mixed micelle, physical crosslinks between polymer chains are formed, and a dramatic increase in solution viscosity is observed. As surfactant concentration increases, comicellar bridging between HM chains becomes unfavorable due to

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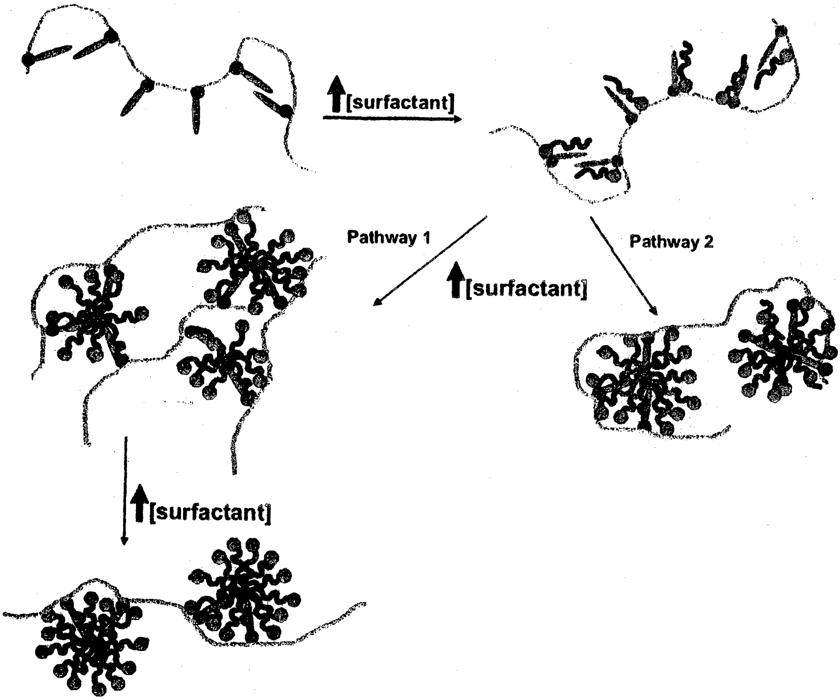
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Pathway 1
[surfactant]
Pathway 2
[surfactant]

Figure 8. Proposed mechanisms of surfactant-induced viscosity modification in HM polymer solutions.

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stoichiometry of the system; therefore, the solution viscosity decreases to levels similar to or even lower than that of the original HM polymer solution.

A second mechanism exists in which the electrostatic repulsions of charged hemimicelles adsorbed along the polymer chain may induce chain expansion. This leads to in increase in viscosity below the critical overlap concentration, c^*. However, in some cases, the opposite can be observed when contractions in the hydrodynamic dimensions result from intramolecular associations induced by comicellization (Figure 8, Pathway 2).

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Conclusions

In this chapter we have reviewed general structural features of water-soluble, zwitterionic polymers including polyampholytes and polybetaines. Solution behavior including stimuli-responsiveness to changes in solution pH and electrolyte concentration has been discussed in terms of polymer composition. Given the number of synthetic procedures and the variety of monomers now available, it may be anticipated that polyzwitterioinc polymers will be increasingly utilized in applications including formulation of personal care items and pharmaceuticals, and for responsive fluids in oil field, mining, and water remediation.

Acknowledgments

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Chapter 4

Synthesis, Aqueous Solution Properties, and Biomedical Application of Polymeric Betaines

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General synthetic procedures for the synthesis of betaine monomers and polymers are outlined. Additionally, the general features regarding the aqueous solution behavior of this class of water-soluble polymer are highlighted. Finally, the use of polymeric betaines in biomedical applications are discussed.

Introduction

Polymeric betaines, or polybetaines, are a subclass of polyzwitterion with polyampholytes representing the other major type of such materials. The fundamental difference between these types of polyzwitterion lies in the charge distribution. In the case of polyampholytes the cationic and anionic (or potentially charged) functional groups reside on ***different*** monomer units, for example a statistical copolymer of acrylic acid with 4-vinylpyridine, whereas for polybetaines the charged groups are on the ***same*** monomeric building block.

Polybetaines may be further distinguished based on the chemical structure of the charged functional groups. In all cases, for synthetic polybetaines the

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cationic species is a quaternary ammonium group and is thus permanently charged. The anionic functionality may be a carboxylate (carbo or carboxybetaines), a sulfonate (sulfobetaines), a phosphate, phosphonate, or phosphinate (phosphobetaine), or can be enolate based, as in the dicyanoetheneolate derivatives. The general chemical structures of these betaine derivatives are shown in Figure 1. The fundamental characteristics of the betaine functionality have been discussed by Laughlin. (*1*)

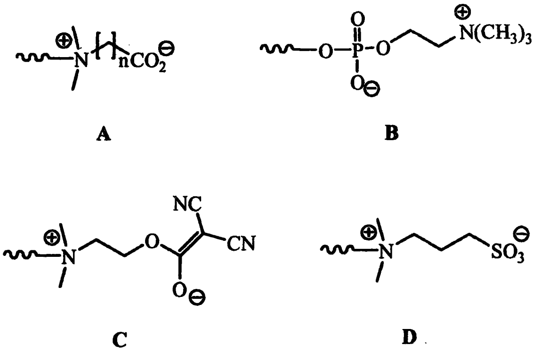

Figure 1. *General betaine structures – carboxy- (A), phospho- (B), dicyanoetheneolate (C), and sulfobetaines (D)*

Betaine monomers can be prepared employing a variety of chemistries some of the more common of which are shown in Figure 2. The most general method in the case of the sulfo-, carboxy-, and dicyanoethemeolate betaines involves the reaction of a tertiary amine precursor monomer with a sultone, lactone, or dicyanoketene acetal respectively. In the case of the carboxybetaines this is limited to reactions of oxetane-2-one. For higher lactones competitive nucleophilic attack at C=O becomes a problematic side reaction. 1,3-propanesultone (shown in Figure 2) is the most common sultone used for the preparation of the sulfobetaine monomers, although others such as 1,4-butanesultone can also be successfully employed. In the case of the phosphobetaines a polymerizable phospholane is reacted, most commonly, with trimethylamine. A wide variety of carboxybetaine monomers can be prepared by a multi-step procedure involving initial quaternization of a suitable tertiary amine monomer with a haloalkylcarboxylic ester followed by ester hydrolysis to the free acid. While the pathways outlined in Figure 2 are the most common, the examples are not exhaustive and additional synthetic protocols have been established for the synthesis of betaine monomers. (*2-7*)

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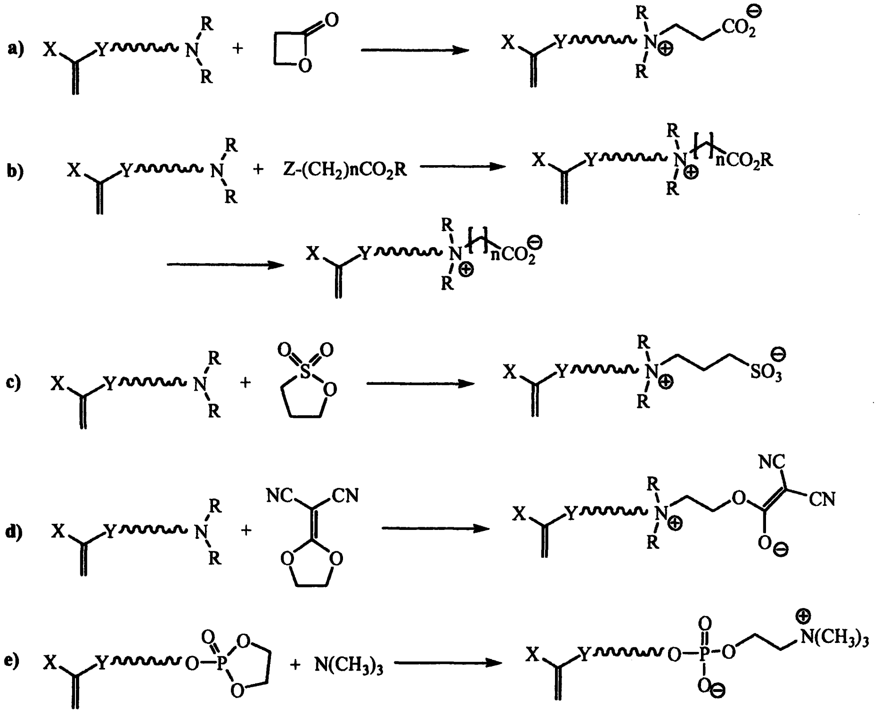

Figure 2. Common synthetic pathways for the preparation of betaine monomers

Synthetic polybetaines were first reported in the 1950's by Ladenheim and Morawetz. (*8*) This first example was a polycarboxybetaine derivative of poly(4-vinylpyridine). The first synthetic polysulfobetaines were reported shortly afterwards by Hart and Timmerman. (*9*) Since these original reports, a very large number of papers have been published describing the synthesis and properties of a wide-range of functional betaines derived from a large number of monomer classes. (*10-20*) Such materials have been almost exclusively prepared via conventional free radical (co)polymerization methodologies. Typically this simply involves the homogeneous solution polymerization of the betaine monomer with or without a comonomer. As such, the resulting (co)polymers are typically poorly-defined materials with high molecular weights, and broad molecular weight distributions. Representative examples of betaine monomers which have been reported in the literature are shown in Figure 3.

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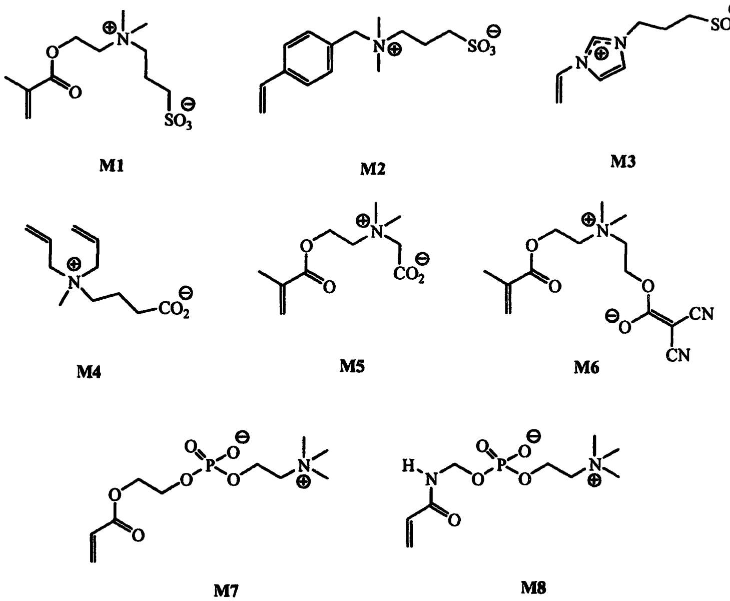

Figure 3. *Examples of betaine monomers reported in the literature*

It has only been within the last 10 years that polymeric betaines with controlled molecular architectures and narrow molecular weight distributions have been prepared. The first report described the synthesis of a series of homopolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) prepared via group transfer polymerization (GTP). These narrow molecular weight distribution materials were subsequentrly converted to the corresponding polysulfopropylbetaines by reaction of the tertiary amine functionality with 1,3-propanesultone. (*21*) A combination of NMR spectroscopy and elemental microanalyses indicated quantitative conversion to the polybetaine. This initial disclosure was followed by several additional reports in which hydrophilic/hydrophobic and hydrophilic/tunably-hydrophilic/hydrophobic block copolymers, also prepared by GTP, were modified post-polymerization to the corresponding sulfopropylbetaine materials. (*22-24*) For example, AB diblock copolymers of DMAEMA with various tertiary amine-containing methacrylic comonomers, such as 2-(diethylamino)ethyl methacrylate (DEAEMA), 2-(diisopropylamino)ethyl methacrylate (DiPAEMA), and 2-(*N*-morpholino)ethyl methacrylate (MEMA), were prepared and subsequently *selectively* derivatized with 1,3-propanesultone at the DMAEMA residues. The ease/rate at which the tertiary amine residues react with 1,3-propanesultone is related to the substitution pattern, i.e. steric crowding, about N. The more sterically hindered monomers (DEAEMA, DiPAEMA, and MEMA) do not react

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with 1,3-propanesultone under the facile conditions which can be employed for the moidification of the DMAEMA residues. (*23*)

Recently, and by virtue of the development of the controlled/"living" free radical polymerization methodologies, various research groups have described the *direct* polymerization of a range of betaine monomers in a controlled fashion. At present both atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization have proven to be the best suited techniques for such syntheses, given the ability to employ such techniques under relatively mild conditions in an aqueous environment. (*25*) For example, 2-(methacryloyloxy)ethyl phosphorylcholine (MEPC) has been homo- and copolymerized in aqueous media via ATRP. (*26,27*) Of the two polymerization techniques RAFT has proven to be the more versatile, at least with respect to monomer choice.(*28*) MEPC has also been polymerized under RAFT conditions (*29*) as has the corresponding acrylate analog (AEPC). (*30*) A larger range of sulfobetaine monomers have been polymerized by RAFT with styrenic, methacrylate and acrylamido derivatives, all having been successfully prepared. (*28*) In addition to simple homopolymers, both AB, ABA and BAB block copolymers of acrylamido sulfobetaine derivatives with N,N-dimethylacrylamide (DMA) and N-isopropylacrylamide (NIPAM) have also been reported. (*31,32*) Carboxybetaines have been polymerized by ATRP. (*33*) At present there are no literature reports detailing the direct polymerization of dicyanoetheneolate betaine monomers by controlled/"living" free radical polymerization.

In addition to the application of the chain-growth processes briefly outlined above, step-growth polymerization has been employed for the preparation of betaine polymers. In particular, numerous examples of phosphobetaines have been prepared using this synthetic approach. For example, Umeda and co-workers described the synthesis of linear polymers of general structure A, Figure 4. (*34*) These were prepared from the reaction of N,N,N',N'-tetramethylhexamethylenediamine with an appropriate bis-dioxaphospholane. Additionally some more 'exotic' polybetaines are known such as those derived from phosphazenes. (*35*)

Aqueous Solution Properties of Polybetaines

The behavior of polybetaines in aqueous media can be very varied, and at times very complex, depending on the type of polybetaine being studied. Indeed, polybetaines are excellent examples of stimuli-responsive materials which are capable of undergoing both reversible conformational changes and phase transitions in response to certain applied stimuli - in particular changes in pH

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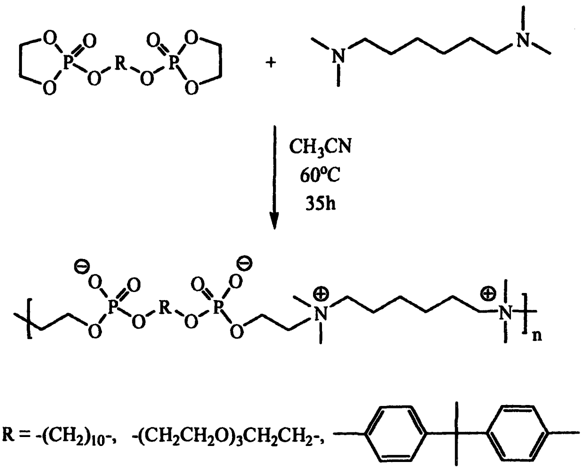

Figure 4. *Synthesis of phosphobetaines with the charge located in the backbone of the polymer*

and/or electrolyte concentration. Unlike polyelectrolytes, the vast majority of polybetaines are ***insoluble*** in pure water. Even though polybetaines are electrically neutral there exists net attractive forces between the functional groups. This results in the formation of a 3D ionically cross-linked network and hence insolubility (the electrostatic forces are greater than the osmotic forces which would draw solvent into the network and facilitate dissolution). However, the addition of a critical concentration of low molecular weight electrolyte will typically induce dissolution. The small electrolyte ions penetrate the ionic network and screen the net-attractive interactions, facilitating molecular dissolution. Such behavior is completely reversible – removal of the electrolyte (by dialysis for example) results in precipitation, i.e. reformation of the ionic network. Thus, polymeric betaines are capable of undergoing phase transitions as a function of salt concentration. Once in solution the polybetaine will continue to respond to further increases in salt concentration, however, the response is now of a conformationl type. Specifically, and in contrast to polyelectrolytes, the polybetaines will chain-expand with increasing salt concentration. Since this is opposite behavior to that exhibited by polyelectrolytes, it has been termed the ***anti-polyelectrolyte effect***. (*36*) For high molecular weight polymeric species such behavior is readily observed by measuring the changes in solution viscosity as a function of salt concentration, Figure 5. This is a general effect which is oberserved for polybetaines.

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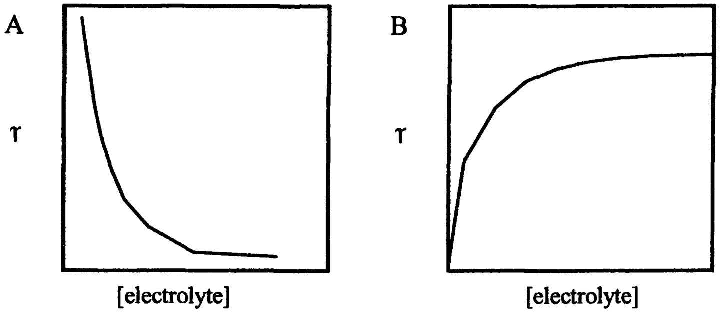

Figure 5. *Classic polyelectrolyte (A) and anti-polyelectrolyte (B) behavior in aqueous media as a function of salt concentration, as monitored by solution viscometry*

The critical salt concentration (CSC) required for initial dissolution and the concentration at which maximum chain expansion occurs does show some dependence on the nature of the salt as well as the polybetaine. (*37*) For example, in their studies of the aqueous solution properties of a poly(vinyl imidazolium sulfobetaine), (*38*) Salamone and co-workers found that dissolution behavior and measured reduced viscosity value of the homopolymer in aqueous media were dependent on the type and concentration of added salt. In the case of a common cation (K^+), the CSC required for dissolution increased in the order F^- (insoluble) > Cl^- (0.38 M) > NO_3^- (0.17 M) > Br^- (0.13 M) > I^- (0.05 M) > ClO_4^- (0.03 M). For a common anion (Cl^-) the CSC increased in the order NH_4^+ (0.52 M) > Li^+ (0.50 M) > Na^+ (0.37 M) > K^+ (0.38 M). Given the data, it is evident that anions have a greater effect on solubility characteristics than the cations. It is clear that salts with anions of small charge/radius ratios are better solubilizers than anons with large charge-radius ratios.

The aqueous solution behavior of polycarboxybetaines can be much more complex given the weakly acidic nature of the carboxylate functional group. With a pK_a of ~4-5, the solution behavior for this class of polybetaine also shows some dependence on the solution pH. Above the pK_a, such (co)polymers exist in the betaine form and behave as expected for this class of materials. However, below this pK_a, when the carboxylate group becomes protonated, the (co)polymer is no longer zwitterionic but rather is cationic. Under these conditions the aqueous solution behavior is typical of a 'traditional' cationic polyelectrolyte. (*39*)

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Several research groups have taken advantage of the aqueous solution characteristics of polybetaines and designed/synthezied materials which are capable of undergoing supramolecular self-assembly in water, forming micellar structures in which the betaine component resides in the corona or in the core. (*24,31*) For example, early reports described the self-assembly of AB diblock copolymers comprised of **M1** (Figure 3) with various hydrophobic alkyl methacrylate comonomers such as methyl methacrylate. (*22,24*) Precursor AB diblock copolymers of DMAEMA with the alkyl methacrylate comonomer were prepared via sequential monomer addition under GTP conditions. Post-polymerization reaction of the DMAEMA residues with 1,3-propanesultone yielded the target sulfopropylbetaine block copolymers, Figure 6A.

Molecular dissolution of these hydrophobic/hydrophilic block copolymers in the non-selective organic solvent 2,2,2-trifluoroethanol (TFE) followed by dilution with aqueous salt – a selective solvent for the betaine block (to yield a final copolymer concentration of 1 wt %) resulted in the supramolecular self-assembly of the block copolymers to form spherical micelles in which the hydrophobic alkyl methacrylate block formed the core and the hydrophilic sulfopropylbetaine the corona (Figure 6B). At a concentration of ca. 10^{-4} M, NaCl micelles with hydrodynamic sizes of ~16.0 nm were observed. Increasing the NaCl concentration resulted in an increase in the observed hydrodynamic diameter upto a maximum of ~26.0 nm at 0.1 M NaCl (Figure 6C). This increase in size was attributed to the antipolyelectrolyte effect, i.e. chain expansion of the coronal chains with increasing electrolyte concentration. In addition to forming block copolymer micelles in which the betaine block resides in the corona, it is possible to prepare micellar aggregates in which the betaine species resides in the core. For example AB diblock copolymers of DMA and 3-[2-(*N*-methylacrylamido)-ethyldimethylammonio]propanesulfonate (MAEDAPS), Figure 7, are stimuli-responsive materials in which the DMA residues are permanently hydrophilic while the MAEDAPS is tunably hydrophilic/hydrophobic by virtue of the phase response to changes in salt concentration. As such, in aqueous media at some critical salt concentration, the block copolymer exists as unimeric, molecularly dissolved polymer chains. Removal of the salt by dialysis renders the MAEDAPS block hydrophobic and the AB diblock copolymer will self-assemble forming nano-sized aggregates, i.e. star micelles, with the betaine residues now located in the *core*, stabilized by a hydrophilic DMA corona. This behavior is completely reversible – addition of low molecular weight electrolyte results in dissociation of the micelles and block copolymer dissolution. Such behavior can be extended to ABA triblock copolymers, resulting in the formation of flower micelles, Figure 6. (*31*)

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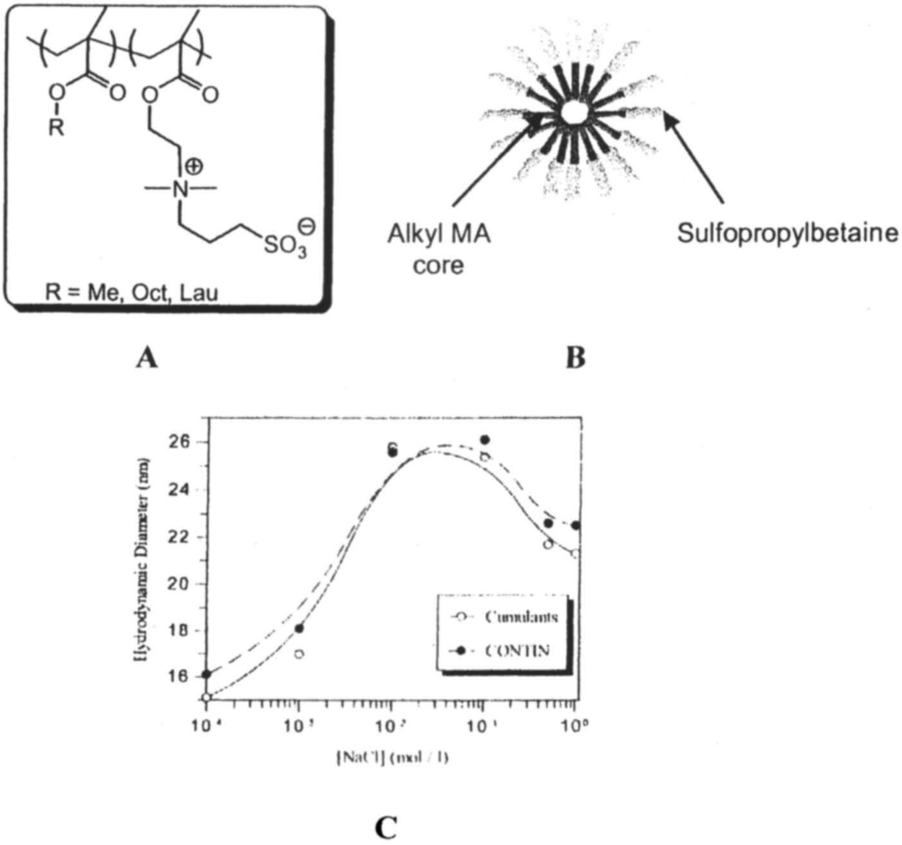
R = Me, Oct, Lau
Alkyl MA core
Sulfopropylbetaine
A
B
Hydrodynamic Diameter (nm)
26
24
22
20
18
16
Cumulants
CONTIN
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
[NaCl] (mol / l)
C

Figure 6. *Generic chemical structure of AB diblock copolymers of an alkyl methacrylate with the sulfopropylbetaines derived from 2-(dimethylamino)ethyl methacrylate (A), representation of a spherical micelle with a hydrophobic alkyl methacrylate core stabilized with a sulfobetaines corona (B), and the change in hydrodynamic diameter as a function of [NaCl] for a 29:71 (mol %) methyl methacrylate:sulfobetaines AB diblock copolymer as determined by dynamic light scattering (C).*

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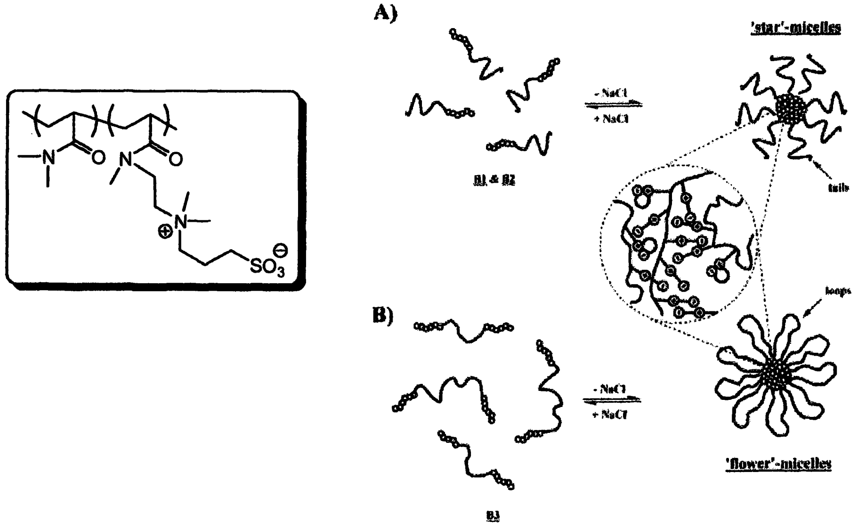

Figure 7. General structure of N,N-dimethylacrylamide-3-[2-(N-methacrylamido)ethyldimethylammonio]propanesulfonate block copolymers and the formation of star (A) and flower (B) micelles as a function of [NaCl]

Biomedical Applications of Polybetaines

One of the interesting features of polymeric betaines is that they mimic certain naturally occurring phospho- and sulfolipids. In particular, such zwitterionic functionality is found throughout the phospholipids located in outer cell membranes, Figure 8. As such, polymeric betaines are good candidate materials for biomedical applications. In particular, such materials are known to act as antiadherents as well as antimicrobials and have found application as coatings for medical implants/instrumentation and as drug delivery vehicles.

The most widely evaluated of the polybetaines with respect to these particular applications have been synthetic phosphobetaines, and in particular MEPC (the methacrylic derivative of **M7**, Figure 3). (*40-44*) One particular area in which copolymers based on MEPC may find application is as coatings for blood filtration devices. For example, Lewis and co-workers (*45*) evaluated copolymers of MEPC with lauryl methacrylate (LMA) of varying molar compositions as coatings for leukocyte filtration material. During such a process it is important that loss of platelets and activation of other blood components be kept to a minimum. Platelet adhesion to the filtration material occurs after initial protein adsorption (this is a prerequisite for platelet adhesion). Therefore minimizing protein interactions with the surface of the filtration membrane will minimize loss of platelets. The statistical copolymers of MEPC/LMA were shown to be haemocompatible with negligible degrees of activated blood

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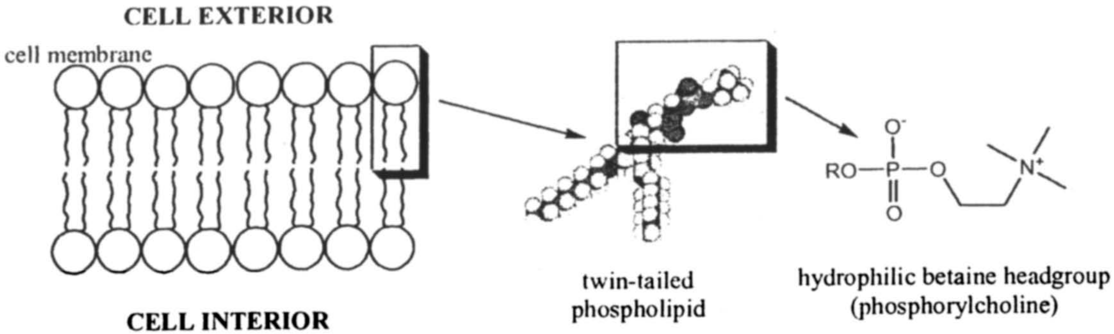
CELL EXTERIOR
cell membrane
CELL INTERIOR
twin-tailed phospholipid
RO—P—O
O⁻
O
N⁺
hydrophilic betaine headgroup (phosphorylcholine)

Figure 8. *Phospholipids/betaines and cell structure*

components adsorbing on the copolymer coated filtration material. Such antibioadherent behavior is one of the key attributes of such phosphobetaine copolymers that renders them attractive biocompatible materials in a wide range of possible areas.

The other classes of polybetaines have been much less studied for biomedical applications, i.e. as antibioadherents. Only recently have polysulfopropylbetaines been examined with respect to this particular property. For example, Lowe et al. examined well-defined statistical copolymers of *n*-butyl methacrylate with the sulfopropylbetaine of DMAEMA, (*46*) as potential antibioadherent coatings. In particular their effectiveness at reducing the bacterial adhesion of *Pseudomonas aeruginosa* onto a poly(methyl methacrylate) (PMMA) substrate was determined. It was shown that when PMMA was coated with the polybetaines that there was a statistically significant reduction in bacterial adhesion vs the uncoated PMMA substrate. While the effect was not extreme, compared to polkyphosphobetaine coatings for example, it seems likely that antiadherence is an intrinsic property of all classes of polybetaines. While a systematic study of polybetaines and their effectiveness as antiadherents has not been conducted, it is probable that any observed differences can be attributed to the relative hydrophilicity of the different betaines functionalities. (*44*)

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Summary/Conclusions

Here we have highlighted some of the synthetic strategies, aqueous solution properties, and one particular application (biomedical) of polymeric betaines. While the general aqueous solution properties of such materials are well-established, recent advances in synthetic methodologies are allowing the preparation of ever-more complex materials capable of exhibiting a rich solution behavior. With the preparation of more sophisticated materials, such highly functional (co)polymers will undoubtly continue to find more advanced applications including those in the biomedical field.

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Chapter 5

Controlled Synthesis of Polymers with Ionic or Ionizable Groups Using Atom Transfer Radical Polymerization

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ATRP is a versatile technique for the preparation of well-defined polymeric materials with polar functional groups. Four strategies to synthesize polymers with ionic or ionizable groups via ATRP are presented: direct polymerization of functional monomers, polymerization of "protected" monomers followed by post-polymerization modification, the use of functional initiators, and end-group chemical transformations. Side reactions that may take place in the direct copper-mediated ATRP of ionic or ionizable monomers conducted in aqueous media include: i) ATRP activator disproportionation, ii) halide ligand loss from the deactivator (the higher oxidation state complex), iii) monomer and/or solvent coordination, iv) loss of halide end groups from the polymeric dormant species, etc. Ways to suppress these reactions are described.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

Introduction

Polymeric materials with ionic or ionizable groups are widely used in the fabrication of ion-exchange resins, superabsorbents, water-purification materials, selective membranes, etc.(1,2) The physical properties of some of these materials can change dramatically upon changes in the environment such as pH, ionic strength, temperature, etc., and they are thus used as "smart" or responsive materials. Block copolymers with two hydrophilic blocks that act as surfactants under certain conditions are attractive materials for crystal engineering.(3) Other applications include coatings, surfactants, adhesives, cosmetics, and controlled drug delivery. These materials are often prepared using radical polymerization due to its tolerance to protic solvents (including water), polar functional groups, and a variety of impurities often encountered in industrial processes. However, conventional radical polymerization does not allow for satisfactory control over molecular weight, composition, molecular architecture, and end-functionality due to the very fast (nearly diffusion-controlled) chain breaking reactions, such as radical coupling and/or disproportionation or transfer.

The past decade has witnessed the discovery and flourishing of various methods of controlled/living radical polymerization (CRP (4)), that allowed for the preparation of polymers with predetermined molecular weight and narrow molecular weight distribution, including a plethora of previously unattainable polymeric materials.(5) The most widely used CRP methods are atom transfer radical polymerization (ATRP (6-8)) reversible addition-fragmentation chain transfer (RAFT (9,10)) polymerization, nitroxide-mediated polymerization,(11,12) and iodine degenerative transfer polymerization.(13)

ATRP is a successful CRP method that has attracted significant attention because of its easy experimental setup, the use of readily accessible and inexpensive catalysts (usually copper complexes of aliphatic amines, imines, or N-containing heterocycles), and simple initiators (alkyl halides, RX). In ATRP, the initiator reacts reversibly with a low-oxidation state metal complex (copper in this text) generating radicals and the corresponding high-oxidation state metal complex with a coordinated halide ligand. The radical can add across the double bond of the monomer (M), giving rise to polymer chains, or with the deactivator (Figure 1; note that all charges of ionic species are omitted for simplicity). Numerous examples of gradient and block copolymers (14) have been reported, as well as polymers with complex architectures, such as polymer brushes,(15) stars,(16) hyperbranched polymers,(17) and hybrids.(18) Some recent results

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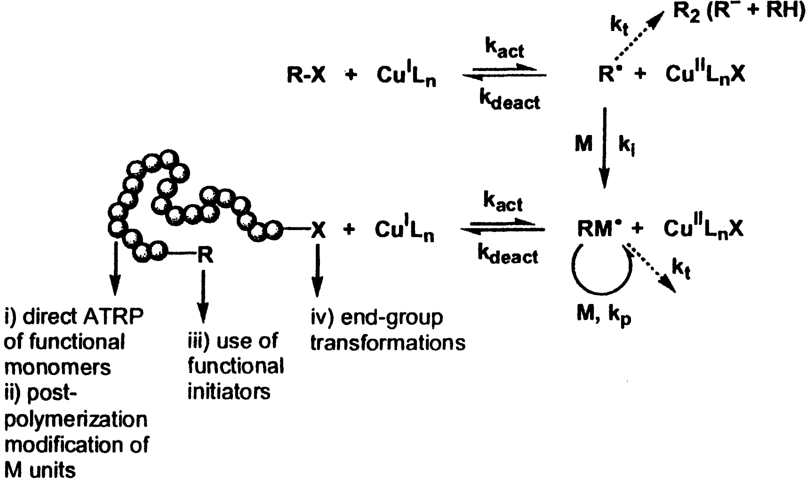
demonstrating the utility of ATRP in the preparation of well-defined (co)polymers with ionic or ionizable groups are presented in this Chapter.

There are four ways to employ ATRP in the synthesis of well-defined polymers with functional groups (Figure 1).(19) The most direct one is the polymerization of a monomer containing the desired functionality. ATRP is generally tolerant of various functional polar groups and this route has been successfully used in many instances. However, in some cases, polar monomers, especially strongly coordinating, basic, or acidic ones, can react either with the ATRP catalyst (leading to its partial or complete deactivation) or the alkyl halide-type initiator or polymeric dormant species (causing loss of functionality in the polymer chains). The synthetic strategy of choice in these cases is to use monomers with "protected" groups that can be transformed into the desired polar functionalites after the polymerization. The use of functional initiators makes it possible to prepare either homo- or heterotelechelic polymers. The polymers produced by ATRP are halogen-terminated, and can be further used as precursors of end-functionalized polymers; a number of nucleophilic substitution reactions have been employed to achieve this goal. Thus, ATRP is an attractive technique for the synthesis of well-defined end-functional polymers. A number of examples of the preparation of functional polymers by ATRP are presented in a recent review paper.(19)



R-X + Cu^{I}L$_n$
k$_{act}$
k$_{deact}$
R$^{•}$ + Cu^{II}L$_n$X
k$_t$
R$_2$ (R$^{=}$ + RH)
M
k$_i$
X + Cu^{I}L$_n$
R
k$_{act}$
k$_{deact}$
RM$^{•}$ + Cu^{II}L$_n$X
k$_t$
M, k$_p$
i) direct ATRP of functional monomers
ii) post-polymerization modification of M units
iii) use of functional initiators
iv) end-group transformations

Figure 1. Preparation of functional polymers by ATRP.

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Direct ATRP of Monomers with Ionic or Ionizable Groups

A number of monomers containing polar functional groups have been successfully polymerized by ATRP. They include 4-vinylpyridine,(20) 2-(*N,N*-dimethylamino)ethyl methacrylate (DMAEMA (21,22)), anionic monomers with carboxylate (23,24) or sulfonate groups,(25-27) cationic monomers (quaternized DMAEMA (25,28)), and some zwitterionic monomers.(29) The ATRP of bio-inspired monomers, containing either short peptide chains(30,31) or nucleobase moieties has also been demonstrated. Most of these polymerizations were carried out in water-containing solvents. It was noticed, however, that ATRP reactions in aqueous media are usually fast, even at room temperature, and the level of control over polymerizations was somewhat poorer than in organic solvents. Some of the side reactions that are responsible for the poor control often observed in aqueous ATRP reactions are presented in Figure 2. They include alkyl halide hydrolysis (or nucleophilic substitution / elimination reactions in the presence of basic monomers), hydrolytic loss of halide ligand from the Cu^{II} halide deactivator,(32) and dipsroportionation of the Cu^{I}-based ATRP activator.(25) To achieve satisfactory control over the polymerization, these reactions should be suppressed or minimized; the last two side reactions are dealt with in this work.

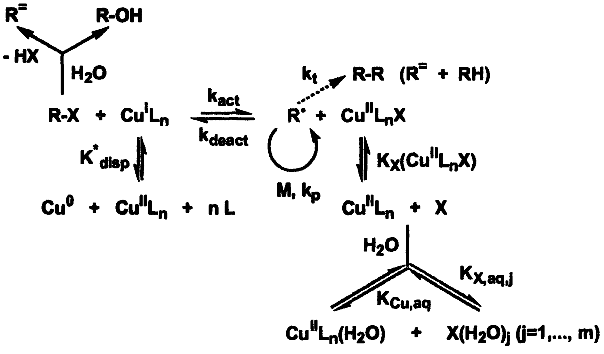

Figure 2. Side reactions in aqueous ATRP. (Adapted from reference 32. Copyright 2004 American Chemical Society.)

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Dissociation of ATRP Deactivators in Protic or Aqueous Media

The rate of an ATRP and the value of the polydispersity index (M_w/M_n, which reflects the level of polymerization control) are given respectively by(7,33)

$$R_p = k_p \frac{k_{act}}{k_{deact}} \frac{[RX]\left[Cu^{I}L_n\right]}{\left[XCu^{II}L_n\right]}[M] \tag{1}$$

$$\frac{M_w}{M_n} = 1 + \frac{k_p[RX]_0}{k_{deact}\left[XCu^{II}L_n\right]}\left(\frac{2}{conv} - 1\right) \tag{2}$$

Both values depend on the concentration of deactivator present in the reaction mixture, which, in turn, depends upon the association constant of halide ion to the $Cu^{II}L_n$ complex (K_X with X = Br or Cl) and the total concentration of $Cu^{II}L_n$ and halide ions in the system, according to eq 3.(32)

$$\left[XCu^{II}L_n\right] = \frac{F - \sqrt{F^2 - 4K_X^2\left[Cu^{II}L_n\right]_{tot}[X]_{tot}}}{2K_X} \quad \left(F = 1 + K_X\left[Cu^{II}L_n\right]_{tot} + K_X[X]_{tot}\right) \tag{3}$$

The value of the equilibrium constant K_X significantly impacts polymerization control. The halogenophilicity of $[Cu^{II}(bpy)_2]^{2+}$ towards both bromide and chloride ions was determined in various protic solvents as shown in Figure 3. The nature of the halide does not significantly affect the K_X value, which however depends on the solvent composition. As the amount of water in the solvent increases from 0 to 27.8 M (corresponding to 0 to 50 vol. %), K_X decreases by about two orders of magnitude. According to eqs 1-3, this leads to fast, poorly controlled, polymerizations. In water-poor mixed solvents, the control over polymerization is significantly better. Unfortunately, the number of ionic monomers that are soluble in such solvents is rather limited and alternative ways to improve the deactivation efficiency in ATRP in aqueous media have to be used. Inspection of eq 3 shows that the use of ATRP catalysts that contain initially relatively large amounts of deactivator or the addition of extra halide salts (such as NaCl, tetrabutylammonium bromide, etc.) should lead to "regeneration" of the deactivator lost by dissociation. Indeed, although ATRP in organic solvents can slow down or even cease when a large amount of Cu^{II} complexes is present, relatively fast ATRP reactions can be carried out in homogeneous aqueous media under these conditions. This is because, in protic media, only a fraction of the Cu^{II} complexes are present in the active form,

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$XCu^{II}L_n$. An example of a procedure for improving the control in ATRP reactions in the presence of halide ions is given below (Figure 6).

The use of a large amount of deactivator (60 % of the total copper) allowed preparation of well-defined poly(2-hydroxyethyl methacrylate) (polyHEMA), which due to the high degree of chain end functionalization was successfully chain-extended with DMAEMA (Figure 4a) yielding a double hydrophilic block copolymer with an ionizable segment.(34) The DMAEMA block can become cationic by protonation or alkylation (Figure 4b), and thus, (co)polymers with ammonium groups can be synthesized.

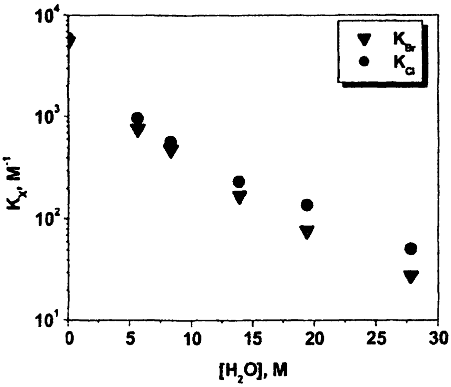

Figure 3. Association constants (halogenophilicity) of $[Cu^{II}(bpy)_2]^{2+}$ *in methanol-water mixtures. (Adapted from reference 32. Copyright 2004 American Chemical Society.)*

Disproportionation of Cu^I Complexes in Aqueous Media

The compounds of Cu^I are generally unstable in aqueous media and tend to disproportionate. For instance, the disproportionation of non-complexed Cu^I ion in water is characterized by an equilibrium constant as large as $K_{disp} = 10^6$.(35) Addition of a ligand L able to form complexes with either Cu^I or Cu^{II} (or with both) can significantly affect the equilibrium constant, which changes to a new value, K^*_{disp}, termed *conditional disproportionation constant,* which is determined by the relative stabilization of the two oxidation states upon coordination. For the case of ligands forming 1:1 complexes with Cu^I and Cu^{II} (with stability constants β^I_L and β^{II}_L, respectively), the value of K^*_{disp} is given by(25)

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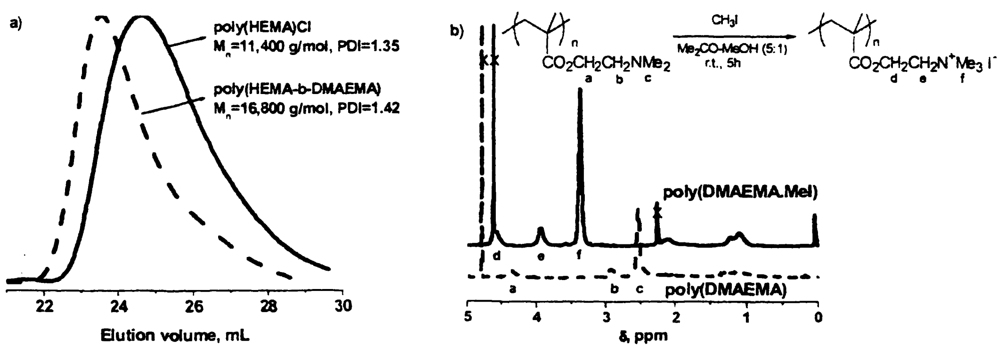

Figure 4. a) Chain extension of polyHEMA macroinitiator with DMAEMA; b) preparation ofpolymers with ammonium goups.(34)

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

$$K^{\bullet}_{disp} = \frac{\beta^{II}_{L}}{\left(\beta^{I}_{L}\right)^{2}[L]} K_{disp} \qquad (4)$$

It is known that the activity of copper-based ATRP catalysts depends upon the redox properties of the complex,(7) which is determined by the ratio of $\beta^{II}_{L}/\beta^{I}_{L}$. The requirement for an ATRP catalyst to perform well in aqueous solvents is high activity accompanied by low propensity for disproportionation. A "map" for catalyst selection can thus be constructed (Figure 5).

Based on Figure 5, it can be predicted that a ligand such as *N,N,N'N",N"*-pentamethyldiethylenetriamine (PMDETA) cannot be used in aqueous copper-madiated ATRP due to very significant disproportionation of the complex Cu^{I}/PMDETA. However, the structurally similar *N,N,N',N",N''',N'''*-hexamethyltriethylenetetramine (HMTETA) is a suitable ligand producing a very active, yet stable towards disproportionation, catalyst. In order to suppress catalyst diproportionation in aqueous media, cosolvents stabilizing Cu^{I} vs. Cu^{II} can be employed. Suitable solvents include pyridine or acetonitrile. It has been reported that the ATRP of sodium 4-styrenesulfonate can be carried out in aqueous methanol;(26,27) no disproportionation of the catalyst was observed under these conditions. Using pyridine as a cosolvent in the aqueous ATRP of DMAEMA quaternized with ethyl bromide (DMEABr) or with methyl trifluoromethanesulfonate (TMAETf) allowed for complete suppression of the disproportionation reaction that takes place in pure water.(36) Figure 6 shows the kinetc results as well as the evolution of molecular weights with conversion in the ATRP of DMEABr and TMATf. As expected (see the discussion in the previous Section), the polymerization was faster and the control poorer in the water-rich solvents. In a given solvent (fixed K_X), the polymerization of the monomer with a bromide counterion was slower and better controlled than that of the trifluoromethanesulfonate monomer, due to the presence of large concentration of halide ions that suppressed the dissociation of the deactivator.

In summary, the copper-based ATRP catalyst can be deactivated in protic solvents via dissociation or disproportionation. These side reactions have been quantitatively described which makes it possible to predict the reaction conditions leading to optimal results in the controlled radical polymerization of variety of water soluble monomers in protic solvents.

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Incorporation of Ionic Groups by Postpolymerization Modification

In many cases, due to the incompatibility of certain functional groups with the ATRP reaction components, protection group chemistry has to be employed. For instance, phenols can reduce the deactivating Cu^{II} halide complexes leading to fast and poorly controlled polymerization, and consequently the direct ATRP of phenol-type monomers is complicated. The ATRP of a protected phenol, 4-acetoxystyrene,(37) catalyzed by CuBr/bpy, however, was well-controlled and was used to prepare polymers with phenol hydroxyl groups.

Acidic monomers such as (meth)acrylic acid, the isomeric vinylbenzoic acids, or unsaturated sulfonic or phosphonic acids protonate and "destroy" the complexes of N-based ligands typically used as ATRP catalysts. Thus, protected acidic monomers are usually polymerized. Protective groups include *t*-butyl,(38) benzyl (deprotection is achieved by hydrogenolysis),(39,40) tetrahydropyranyl, (39,40) 4-nitrophenyl,(41) and 1-ethoxyethyl (deprotection is achieved by heating to 160 °C).(42)

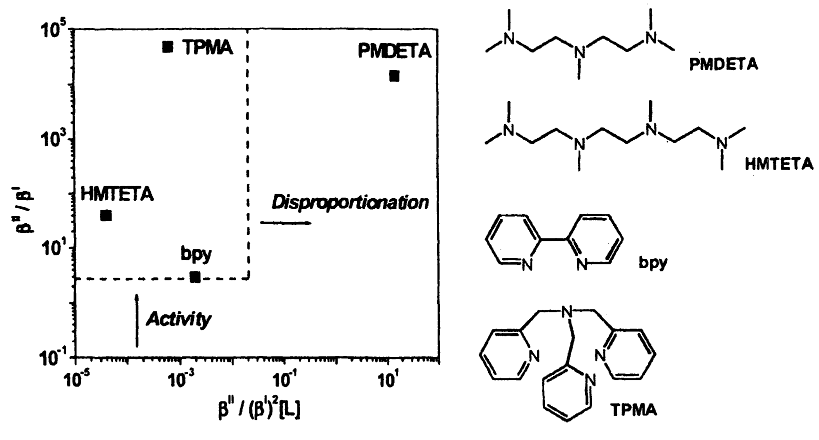

Figure 5. Map for the rational selection of catalysts suitable for aqueous ATRP. The structures of the ligands are given on the right.

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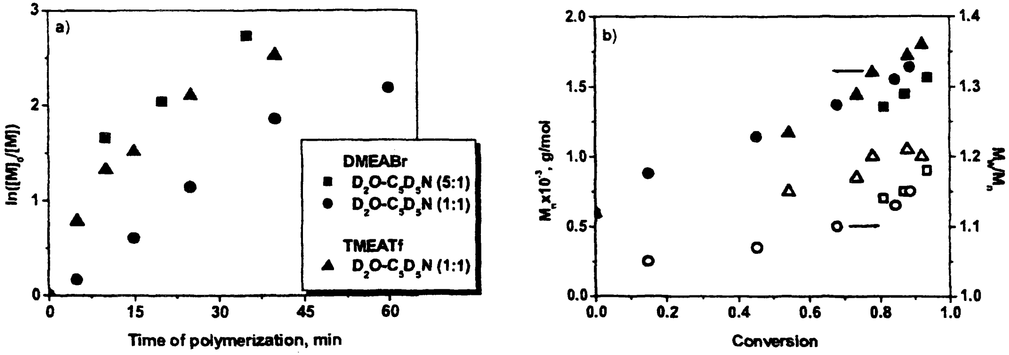

Figure 6. Kinetics (a) and molecular weight evolution (b) in the ATRP of DMEABr (squares and circles) and TMATf (triangles) in water-pyridine mixtures at 25 °C using a CuBr + 20% $CuBr_2$ / bpy as the catalyst and poly(ethylene oxide) methyl ether 2-bromoisobutyrate as the initiator. Targeted DP = 100.(36)

Tetrazoles are acidic (resembling carboxylic acids) coordinating compounds and the direct ATRP of 5-vinyltetrazole (5VT) has not been reported. The preparation of well-defined tetrazole-containing polymers could be accomplished using the atom transfer radical (co)polymerization of acrylonitrile,(43,44) AN, followed by a "click" chemistry-type of chemical modification, shown in Figure 7.(45) Homo- and copolymers (both random and block) with the acidic tetrazole units were successfully synthesized.

Another functional ionizable group of interest, that cannot be incorporated directly in a polymer prepared by ATRP is the primary amino group. However, reduction of the easily accessible AN-containing (co)polymers with $LiAlH_4$ leads to polymeric materials with primary amino groups. This reaction was employed in the reduction of random styrene-acrylonitrile (SAN) copolymers and, as shown in Figure 8, it produced a well-defined ionomer containing allylamine units.(34)

The use of click-type chemical modifications (46) based on the Cu^I-catalyzed Huisgen addition (47) of azides to alkynes is a very promising approach to functional polymeric materials. These high-yield reactions are easily performed at ambient temperature. Recently, it was demonstrated that well-defined poly(3-azidopropyl methacrylate) prepared by ATRP reacts with a variety of substituted acetylenes including ones with carboxylate or phosphonium groups to yield the corresponding polyelectrolytes.(48)

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Use of Functional Initiators and End-Group Chemical Transformations

In some cases, it may be necessary to incorporate only one or a few ionizable groups at the polymer chain end. To synthesize such telechelic polymers, various functionalized ATRP initiators have been used. Interestingly, the acidic initiator 4-carboxybenzyl bromide was demonstrated to yield well defined polymers with a carboxylic acid group.(49) No protection-deprotection chemistry was needed. A biotin-containing ATRP initiator is an example of functional initiator derived from a biologically important molecule; it is of interest since it yields polymers reacting specifically with avidin.(50)

An ionizable functional group that is particularly difficult to incorporate in polymers prepared by radical polymerization is the thiol group because thiols are well-known chain transfer agents. However, we have recently demonstrated the synthesis of (bio)degradable linear polymers and gels, derived from styrene and

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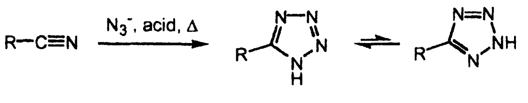

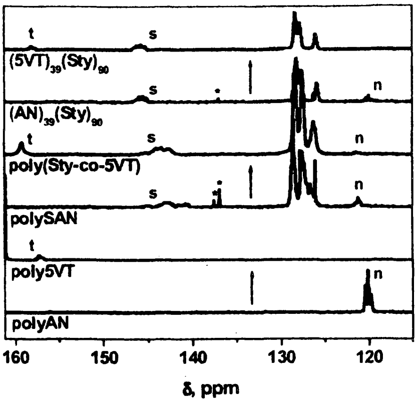

Figure 7. ^{13}C NMR spectra of AN (co)polymers (spectra 1, 3, and 5 from bottom to top) and of polymeric tetrazoles prepared there from (spectra 2, 4, and 6). The signals of the quaternary carbon atoms from the tetrazole and Sty rings are designated with "t" and "s", respectively, and from the nitrile group – with "n". Impurity signals are marked with an asterisk. SAN is a random copolymer of AN with styrene (Sty), containing ca. 37 mol % of AN units. (Reproduced from reference 45. Copyright 2004 American Chemical Society.)

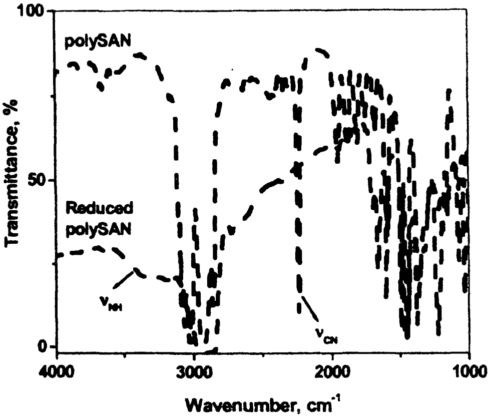

Figure 8. IR spectra of a SAN copolymer and the product of its reduction by $LiAlH_4$.(34) Note the disappearance of the nitrile band.

methacrylates, containing the disulfide group.(51,52) Upon reduction with dithiothreitol or tributylphosphine, thiol-terminated polymers were obtained in excellent yields. The acidic and coordinating thiol group can also be incorporated in polymers prepared by ATRP by using nucleophilic substitution reactions of the terminal halogen atom(s) with sulfur-based nucleophiles such as thiodimethylformamide (51) or thiocarbamide.(53)

Polymers prepared by ATRP are halogen terminated and can therefore participate in numerous nucleophilic substitution reactions. An early example was the preparation of azido-terminated polymers, which served as precursors of primary amino-terminated polymers (after reduction with tributylphosphine).(54) Another example is the reaction of bromine-terminated polymers with tributylphosphine yielding polymers with a phosphonium salt type of end-group.(55) The utility of click chemistry has already been demonstrated by us (56) and by others,(57-62) and it can be envisioned that this will become one of the widely used strategies to prepare end-functionalized polymers.

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Conclusions

Various synthetic strategies involving ATRP are presented for the synthesis of functional polymers of controlled molecular weight and narrow polydispersity containing ionic or ionizable groups. These strategies are based either on the direct ATRP of functional monomers, or a combination of ATRP and postpolymerization modifications, which can affect every monomer unit or only the end-groups. Some recent examples illustrating the utility of ATRP are presented.

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Chapter 6

Reversible Addition Fragmentation Chain Transfer Polymerization of Water-Soluble, Ion-Containing Monomers

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Reversible addition-fragmentation chain transfer (RAFT) polymerization has been the focus of extensive research over the last several years. RAFT allows for the tailoring of polymers with complex architectures including block, graft, comb, and star structures with predetermined molecular weights, end group functionality, and narrow molecular weight distributions. In this chapter we present an overview of the synthesis and solution properties of water-soluble, ion-containing monomers synthesized via RAFT.

Introduction

During the past decade, advances in controlled radical polymerization (CRP) techniques have resulted in the synthesis of well-defined polymers with diverse architectures and structural features *(1-3)*. Among the most successful are stable free radical polymerization (SFRP), atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain transfer (RAFT) polymerization. In general, these methods allow for similar levels of control as compared to traditional living techniques while possessing the versatility and robustness of conventional free radical polymerizations.

RAFT operates on the principle of degenerative chain transfer and as such differs fundamentally from both SFRP and ATRP. Optimization of a RAFT polymerization relies on the appropriate choice of chain transfer agent (CTA). These are thiocarbonylthio species generally belonging to one of the following families of compounds: dithioesters, xanthates, dithiocarbamates, and trithiocarbonates, *(4-11)* Figure 1.

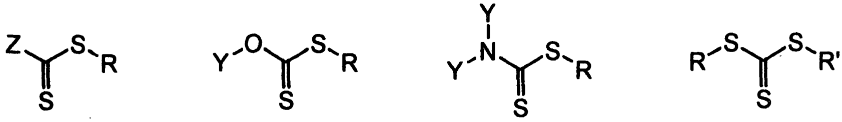

Figure 1. General structure of common thiocarbonylthio RAFT-agents.

RAFT agents are prepared by a number of chemical procedures and are the subject of numerous publications *(4,13-14,119)*. It should be noted that it is important to match the RAFT CTA with the appropriate monomer to achieve a controlled polymerization. For this reason, RAFT agents have been prepared to address issues concerning the polymerization of certain hydrophilic monomers *(15-19)*.

A major advantage of RAFT technology is the wide range of functional monomers that can be polymerized in a controlled fashion. To date, RAFT has been successfully employed in the polymerization of hydrophilic nonionic, *(8, 15-16,19-20,22-44,119)* cationic, *(14,20,39,41,46,47,119)* anionic *(11,20,26,44, 48-55,119)* and zwitterionic (betaine) *(28,44,56-59,119)* monomers from a range of monomer classes in both aqueous and organic media.

The ability to prepare water-soluble polymers with a high degree of functionality either directly in water or in organic media is particularly noteworthy. To date, RAFT has proven to be the most facile polymerization technique for the homogeneous aqueous polymerization of hydrophilic monomers in a controlled manner *(121-122)*. The aim of this chapter is to highlight the synthesis of novel water-soluble, ion-containing (co)polymers in both aqueous and non-aqueous media.

Ion-containing polymers are polymers with charged functional groups attached to the polymer chain. These macromolecules are usually classified as polyanions, polycations, and polyzwitterions. Associated with the polyions are counterions of the opposite charge in sufficient numbers to maintain neutrality *(60)*. Water-soluble polyelectrolytes and polyampholytes exhibit a number of common traits with water-soluble nonionics. However, differences arise from the presence of charges on the macromolecular backbone and more mobile counterions electrostatically bound to an extent determined by p*K*a, solvent, and

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local dielectric effects. Generally, phase behavior and enhanced solubility result from increased segmental hydration and increased free energy of mixing. Both polyelectrolytes and polyampholytes have been studied extensively because molecular structures can be tailored to allow large conformational changes with pH, temperature, or added electrolytes. The conformational changes in response to these stimuli can also be utilized to trigger supramolecular self-assembly in responsive block copolymers.

Cationic (Co)polymers via RAFT

Cationic polymers are of interest due to their varied physical and chemical properties. They have been evaluated for a wide range of applications including water purification, antimicrobial coatings, additives for cosmetics, and gene vectoring agents. Controlled cationic polymers have been prepared by a large number of techniques including anionic, *(61-66)* group transfer, *(67-74)* SFRP, *(75, 76-78)* ATRP, *(79-84)* and ring opening metathesis (ROMP) *(86-87)* polymerization. Cationic or potentially cationic polymers have also been prepared via RAFT *(24, 39, 46-47, 88, 121-122)*. Figure 2 shows typical chemical structures of amine-containing monomers that have been successfully polymerized under RAFT conditions.

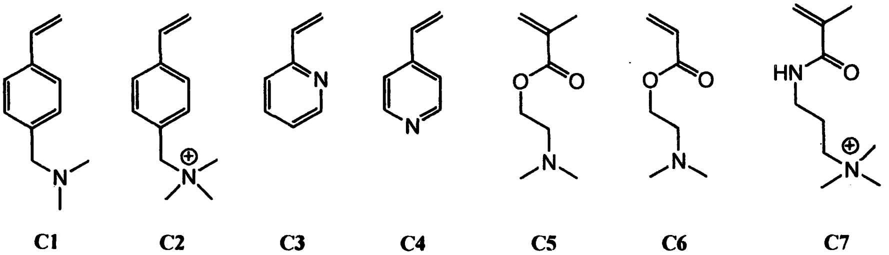

Figure 2. Amine containing monomers which have been polymerized by RAFT.

Styrene Based Cationic (Co)polymers

RAFT–synthesized cationic copolymers were first reported by Mitsukami and Donovan in our group. AB diblock copolymers comprised of *N,N*-dimethylbenzylvinylamine (**C1**) with *ar*-(vinylbenzyl)trimethylammonium chloride (**C2**) were synthesized with CTP and 4,4'-azobis(4-cyanopentanoic acid) V-501 in water at 70 °C. These AB diblock copolymers were capable of

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undergoing reversible self-assembly as a function of solution pH. At low pH, both blocks are hydrophilic and the AB diblock copolymers existed as unimers. Raising the solution pH resulted in the deprotonation of the amine residues in **C1**. In this deprotonated form, the **C1** residues became hydrophobic and the diblock copolymer self-assembled into micelles with hydrodynamic diameters of approximately 40 nm. This process was completely reversible as acidification of the aqueous solution results in a return to unimers *(24)*.

In a subsequent study, Sumerlin *(39)* disclosed the synthesis and aqueous solution properties of AB diblock copolymers of both **C1** and **C2** with *N,N*-dimethylacrylamide (**DMA**). Block copolymers were prepared employing either **C1** or **C2** as the macroRAFT agent for the block copolymerization of **DMA**. This report represented the first example of AB diblock copolymers prepared in aqueous media from dissimilar monomer classes. The AB diblock copolymers of **DMA** and **C1** also exhibit reversible pH-induced self-assembly characteristics in water. These self-assembled micelles can be crosslinked by taking advantage of the reactive tertiary amine residues in the aggregate cores. For example, the addition of α,α'-dibromo-*p*-xylene to an aqueous solution of the micelles led to core crosslinked micelles.

Vinylpyridine Cationic (Co)polymers

Yuan and coworkers *(46)* and Convertine, *(47)* were the first to report the RAFT polymerization of vinylpyridines. Yuan described the use of dibenzyl trithiocarbonate as the RAFT CTA for the synthesis of block copolymers of styrene and 4-vinylpyridine (**C4**). Polymerizations were conducted in DMF at 60, 80, or 110 °C using AIBN as the source of primary radicals. Both polystyrene and poly**C4** homopolymers were prepared and subsequently employed as macro RAFT agents. Block copolymerizations appeared to proceed smoothly with resulting polydispersities in the range 1.09-1.24. The authors also demonstrated the ability of these triblock copolymers to undergo self-assembly in water by virtue of the hydrophobic nature of the polystyrene block. Both spherical micelles and rods were formed with the morphology being dependent upon the block copolymer compositions.

Concurrently, Convertine reported the controlled polymerization of both 2- and 4-vinylpyridine (**C3** and **C4**) as well as AB diblock copolymers synthesized from the two monomers *(47)*. The homopolymers were prepared under bulk conditions with cumyl dithiobenzoate (CDB) and AIBN at 60 °C. Both **C3** and **C4** polymerized in a controlled manner as evidenced by the excellent agreement between the theoretical and experimentally determined molecular weights coupled with the low polydispersities (M_w/M_n) expected for a controlled

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polymerization. Further evidence for the controlled nature of these polymerizations was provided by employing **C3** or **C4** as macroRAFT agents for the subsequent block copolymerization with the other monomer. The SEC traces were unimodal and essentially symmetrical, indicating near-quantitative blocking efficiency and little/no evidence of undesirable side reactions such as radical-radical coupling between polymer chains.

(Meth)Acrylamido Cationic (Co)polymers

To date, there are few reports of the synthesis of cationic acrylamido (co)polymers by RAFT polymerization. Our group investigated the aqueous homo- and block copolymerization of *N*-[3-(dimethylamino)propyl] methacrylamide (**C7**). Polymerizations were conducted with 4-cyanopentanoic acid dithiobenzoate (CTP) as the RAFT agent and V-501 as the primary radical source under buffered conditions. Good correlation between the theoretical and experimental molecular weights, linearity of the molecular weight vs. conversion plots, low polydispersities, and the excellent SEC resolution of the macro CTA from the chain extended product and block copolymer with **DMA** demonstrated excellent overall control *(115)*.

Tertiary amine-containing methacrylates have been widely studied and exhibit a varied range of aqueous solution properties *(87)*. Surprisingly, little has been done with the RAFT synthesis of (co)polymers containing this particular group of monomers. The RAFT polymerization of **C5** has been reported in the literature *(20, 45)*, but a detailed examination of the polymerization kinetics has yet to be disclosed. A demonstration of the controlled nature of **C5** homopolymerization was reported by Lowe *et al.* in studies of glycopolymer synthesis *(18)*. Homopolymerization of **C5** under bulk conditions employing CDB with AIBN exhibited all the expected characteristics of a controlled polymerization.

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Anionic (Co)polymers via RAFT

The controlled polymerization of charged monomers by RAFT is not limited to cationic species. A number of anionic (co)polymers have recently been reported utilizing RAFT technology. Typical monomers are shown in Figure 3.

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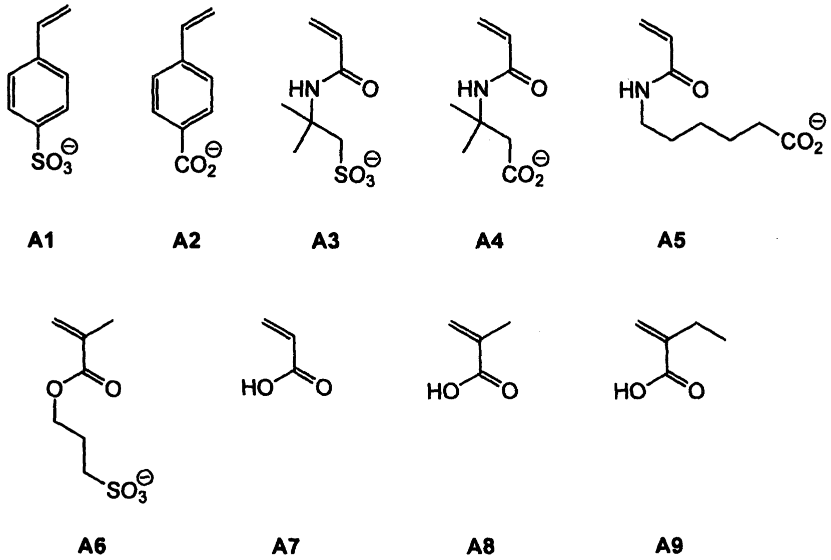

Figure 3. Chemical structures of anionic, or potentially anionic monomers polymerized by RAFT.

Styrene Based Anionic (Co)polymers

The RAFT synthesis of poly(styrene sulfonate) was first reported by Chiefari *et al.* *(45)*. The authors demonstrated that sodium 4-styrenesulfonate, (**A1**), could be polymerized directly in water employing CTP and V-501 at 70 °C to yield a homopolymer with an M_n of 8,000 and a polydispersity index of 1.13 at 70 % conversion.

A detailed study concerning the homopolymerization of **A1** and the ability to form AB diblock copolymers with **A2** was conducted by our group *(24)*. **A1** polymerizes rapidly with near-quantitative conversion being observed after ~1-1.5 h. Aqueous size exclusion chromatography (ASEC) confirmed controlled polymerization as evidenced by the close agreement between theoretical and experimental molecular weights as well as the low polydispersities. Also outlined in this paper was a preliminary investigation into the effect of CTA architecture on the homopolymerization of **A1**. Two different water-soluble CTAs were compared, namely CTP and the commercially available carboxymethyl dithiobenzoate. In the case of the CTP-mediated polymerization, an observed M_n of 19,800 with M_w/M_n = 1.17 was determined by ASEC, which is in very close agreement with the theoretical M_n. However, in the case of the carboxymethyl dithiobenzoate-mediated polymerization, an M_n of ~ 500,000 with M_w/M_n = 3.00 was determined by ASEC. This result alone clearly demonstrates the need for a judicious choice of CTA in order to achieve control in RAFT polymerizations.

Later studies *(24)* demonstrated that homopolymers of **A1** could be used as macroRAFT agents for the subsequent block polymerization of **A2.** This facilitated the preparation of pH-responsive block copolymers. At high pH, both blocks are ionized and the block copolymer was molecularly dissolved. However, upon acidification, the **A2** residues were protonated, rendering them hydrophobic and inducing self-assembly into spherical micelles with a hydrodynamic diameter of ~ 19.0 nm (Figure 4). This was behavior analogous to that described above for the **C1/C2** diblock copolymers.

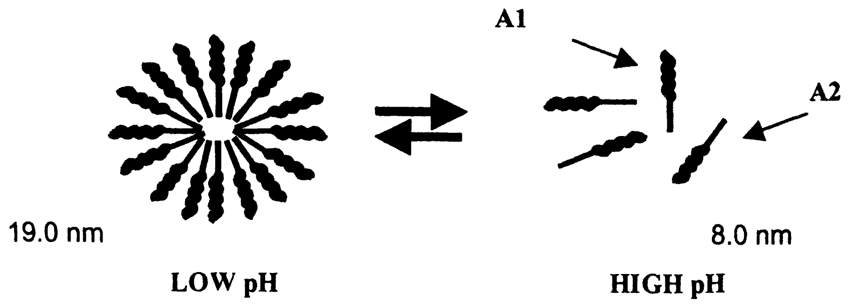

***Figure 4.** Reversible pH-induced self-assembly of A1/A2 diblock copolymers.*

(Meth)acrylamido Anionic (Co)polymers

RAFT is arguably the most facile method for the controlled synthesis of acrylamido-based monomers directly in water *(121)*. The first literature report of anionic acrylamido (co)polymers by Sumerlin involved the controlled polymerization of **A3** and **A4** directly in aqueous media *(52)*. Linear pseudo first-order rate plots were observed following an initial induction period of ~ 60 min. The M_n vs. conversion plots were also linear.

Having shown that both **A3** and **A4** polymerized in a controlled fashion under homogeneous aqueous RAFT conditions, the ability to employ both poly**A3** and poly**A4** as macroRAFT agents for the preparation of AB diblock copolymers was then demonstrated. **A3/A4** copolymers were prepared in both the forward and reverse directions *(52)*. The success of these block copolymerizations was clearly demonstrated in the ASEC traces by a shift to lower elution volume after block copolymerization. Both SEC traces are narrow and unimodal with no evidence of high or low molecular weight impurities.

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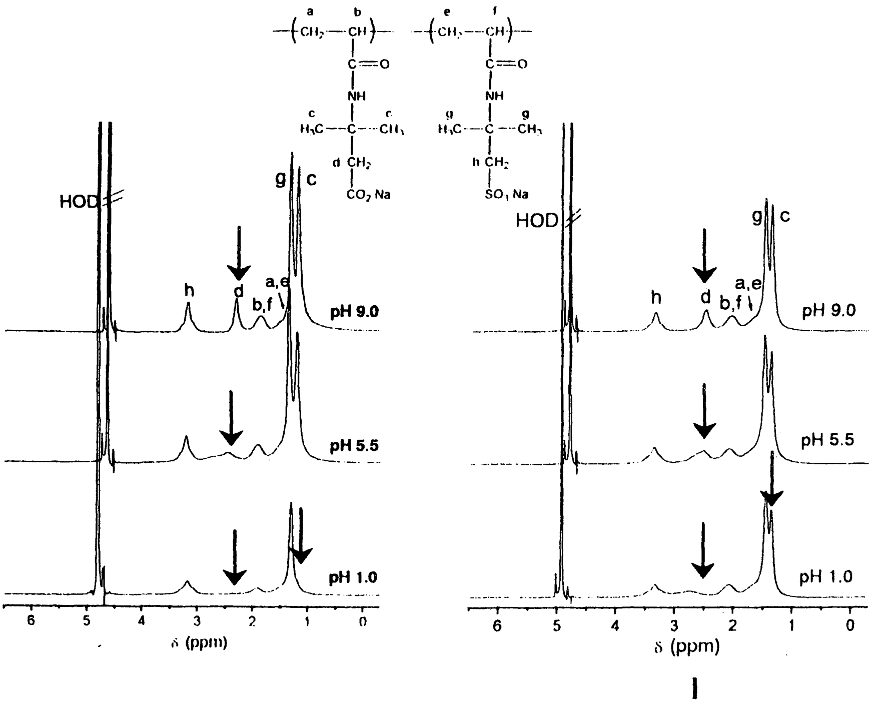

Figure 5. ^{1}H NMR spectra and peak assignments for copolymers of **A3** and **A4** in D_2O as a function of solution pH (adjusted with NaOD or DCl): poly(**A3**-block-**A4**) (A) and poly(**A3**-stat-**A4**) (B).

A3/**A4** diblock copolymers were prepared *(55)* and hypothesized to behave in a similar manner to the **A1**/**A2** copolymers in aqueous media. **A3** is known to be permanently anionic over the common pH range, whereas **A4** has a readily accessible pK_a and is tunable hydrophilic/hydrophobic. A combination of NMR spectroscopy, dynamic light scattering (DLS), and fluorescence measurements confirmed reversible pH-induced micelle formation. For example, Figure 5 shows typical ^{1}H NMR spectra of an **A3**/**A4** block copolymer (A) and an **A3**/**A4** statistical copolymer (B) at selected solution pH values with the relevant peak assignments shown.

At pH 9.0 all peaks associated with both **A3** and **A4** were clearly visible. As the pH was lowered, the **A4** residues underwent protonation rendering them hydrophobic. This induction of hydrophobicity was evident in the NMR spectra and was illustrated by the broadening of the peaks associated with the hydrophobic moieties due to their decreased mobility in aqueous media. Eventually, at very low pH, the peaks associated with the **A4** residues completely disappeared, and only those peaks associated with **A3** were still visible. This behavior is consistent with the hydrophilic/hydrophobic transition of the **A4** residues upon acidification and indicates that for the block copolymer, supramolecular assembly occurred.

Table 1. Hydrodynamic diameters (D_h) as determined by DLS of block and statistical copolymers of **A3** and **A4** as a function of solution pH.

Sample	D_h (nm) pH 9.0	D_h (nm) pH 1.0
PA3$_{70}$	5	4
P(A3$_{70}$-*b*-**A4**$_{62}$**)**	6	25
P(A3$_{70}$-*b*-**A4**$_{40}$**)**	5	24
P(A3$_{70}$-*b*-**A4**$_{25}$**)**	6	21
P(A3$_{70}$-*b*-**A4**$_{16}$**)**	6	18
P(A3$_{106}$-*stat*-**A4**$_{40}$**)**	11	7
P(A3$_{35}$-*stat*-**A4**$_{112}$**)**	11	9
P(A3$_{79}$-*stat*-**A4**$_{89}$**)**	13	9

A DLS study was conducted to examine the effect of pH on size (Table 1). Initially, a poly**A3** homopolymer was examined by DLS at both high and low pH. **A3** remained molecularly dissolved over the entire pH range due to the pH insensitive nature of the sulfonate residues. In regard to the diblock copolymers however, significant differences were observed at the two pH conditions. As expected at high pH, both **A3** and **A4** residues were in their ionic form, sizes consistent with unimers of 6.0 nm were observed. Lowering the pH resulted in an increase in the observed D_h with sizes ranging from 18-25 nm depending on the molar composition. Increasing the mol % of **A4** residues led to an increase in D_h. This is consistent with the hydrophilic/hydrophobic transition of the **A4**

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residues followed by self-assembly. Given the degree of polymerization of the AB diblocks, the measured sizes are typical of micelles.

In related work, Yusa et al. described the synthesis and aqueous solution properties of AB diblock copolymers of **A3** with **A5** or **NIPAM** *(90-91)*. The block co-polymerization of **A5** with a macroRAFT agent derived from **A3** proceeded smoothly as evidenced by the ASEC traces, Mn vs. conversion plots, and pseudo first-order kinetic plots. The resulting AB diblock copolymers were reported to have narrow molecular weight distributions and possessed M_n values of approximately 30,000 (the M_n of the **A3** macroCTA was 19,000). As in the case of the **A3/A4** diblocks described by Sumerlin et al., the **A3/A5** species were sensitive to changes in the aqueous solution pH by virtue of the readily accessible pK_a of the carboxylic acid functional species on **A5**. Using a combination of dynamic and static light scattering, fluorescence spectroscopy and ^1H NMR spectroscopy, Yusa and coworkers reported that the block copolymers existed as micelles at pH < 4.0. At high pH, the macromolecules were in a unimeric state. This self-assembly was shown to be reversible. Similar reversible aggregation was likewise demonstrated for the **A3/NIPAM** *(91)* AB diblocks. However, in this example, the authors took advantage of the readily accessible LCST of the NIPAM block as a means of inducing supramolecular self-assembly.

To date, the only example of a RAFT-produced anionic methacrylate polymer was reported by Lowe and Sumerlin *(36)*. 3-Sulfopropyl methacrylate (**A6**) was block copolymerized with 2-methacryloxyethyl glucoside (MAGlu) to yield novel anionic-glycopolymeric materials. A detailed homopolymerization study of **A6** has yet to be described. However, it was shown that **A6** homopolymerizes in water at 70 °C with the V-501/CTP initiator/CTA combination. The pseudo first-order kinetic and M_n vs conversion plots showed that the homopolymerization of **A6** proceeded in a controlled fashion.

Polymerization of acrylic acid (**A7**) or its neutralized derivative has been attempted with more RAFT agents than any other monomer. As with several other functional monomers, the RAFT polymerization of **A7** was disclosed in the first literature report by Chiefari et al. *(45)*. Here **A7** was polymerized in DMF at a concentration of ~ 3.0 M at 60 °C with 1-phenylethyl dithiobenzoate and AIBN. After 4 h, a homopolymer with an experimentally determined M_n of 13,800 and M_w/M_n of 1.23 (18 % conversion) was observed. In a subsequent paper, Chong and coworkers *(92)* demonstrated the ability to prepare AB diblock copolymers of butyl acrylate (BA) with **A7** employing the same RAFT agent.

The most detailed evaluation regarding homopolymerizations of **A7** is that of Ladavière, Dörr, and Claverie *(50)*. The authors screened 17 RAFT agents including dithioesters, dithiocarbamates, xanthates and trithiocarbonates. Polymerizations were conducted in ethanol at 90 °C employing V-501 as the radical source. In all cases [A7]:[CTA]:[V501] = 50:1:0.1 and [A7] = 2.92

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mol/L. The authors reported the best overall control with either phenoxyxanthate or trithiocarbonate RAFT agents. Building on these observations, Loiseau *et al.* *(49)* conducted a more detailed study of the polymerization of **A7** with two trithiocarbonate CTAs, namely trithiocarbonic acid dibenzyl ester and trithiocarbonic acid bis(1-phenylethyl)ester. Polymerizations were conducted in methanol, ethanol, 2-propanol, and dioxane. Generally, polymerizations were controlled only at low conversions. At high conversions, transfer reactions to solvent were observed. This was most noticeable in the case of 2-propanol but also occurred to a lesser extent with other solvents. As part of this same study, the authors evaluated poly**A7** homopolymers as dispersants for kaolin, $CaCO_3$, and TiO_2.

The effectiveness of trithiocarbonates as CTAs for the RAFT polymerization of **A7** has also been demonstrated by Lai, Filla and Shea. (11) The novel carboxyl-functionalized RAFT agents 2-(1-carboxy-1-methylethylsulfanylthiocarbonylsulfanyl)- 2-methyl-propionic acid (CMP) and 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid (DMP) were shown to work well for **A7** in both organic (DMF) and aqueous media yielding homopolymers with low polydispersity indices and near-quantitative conversion after 6-7.5 h at 70 or 80 °C. In another example of trithiocarbonate-mediated **A7** RAFT polymerization, Hong et al. *(21)* reported well defined, low polydispersity poly**A7** in DMF, dioxane, and in bulk conditions with ^{60}Co irradiation.

Gaillard, Guyot and Claverie *(51)* have also reported the synthesis of **A7**-butyl acrylate (BA) block copolymers employing both xanthate and trithiocarbonate RAFT agents. The authors evaluated these amphiphilic block copolymers as macromolecular surfactants for the emulsion polymerization of BA and methyl methacrylate (MMA). **A7** was polymerized first with target block copolymer compositions (**A7**:BA) of 20:10, 20:20, 20:40, 50:25, and 50:50 (ratios of DP_n). Following a detailed evaluation of the self-assembly properties of the AB diblock copolymers in aqueous media, the authors demonstrated that the materials were indeed effective stabilizers in seeded emulsion polymerizations, thus facilitating the preparation of lattices with up to 50% solids. In related work, Ferguson and coworkers prepared **A7**-BA diblocks mediated by the unsymmetrical trithiocarbonate (2-{[(butylsulfanyl)carbonothioyl]sulfanyl}propionic acid) for ab inito emulsion polymerization *(93)*.

Llauro *et al.* *(94)* analyzed the chain end functionality of poly**A7** prepared with the trithiocarbonic acid dibenzyl ester after treatment with sufficient NaOH to neutralize the **A7** residues and cleave the trithiocarbonate functionality. Surprised at the lack of detectable thiol groups after treatment with NaOH, the authors conducted a detailed analysis employing NMR spectroscopy and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). After careful analysis, the authors were able to identify thiol, disulfide, thiolactone and H-terminated polymer chains.

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More recently, Khousakoun, Gohy, and Jérôme *(96)* reported the synthesis and aqueous solution properties of ABA triblock copolymers of poly(ethylene oxide)-methyl ether methacrylate (PEOMA) (A block) with **A7** (B block) using the trithiocarbonic acid dibenzyl ester RAFT agent and V-501 as the initiating species in *n*-butanol at 90 °C. Interestingly, the "pseudo-triblock" copolymer was prepared by a statistical copolymerization of the two monomers in which the difference in the reactivity ratios was employed to prepare a slightly tapered, blocky structure (the product of the literature-reported reactivity ratios was ~ 1 and as such a blocky-type structure was predicted to result). Due to the sensitivity of the blocks to pH, ionic strength and temperature changes, as well as the dependence of the secondary H-bonding interactions to these environmental changes, the copolymers exhibited complex self-assembly behavior in aqueous solution.

Schilli et al. also studied the synthesis and aqueous solution properties of doubly hydrophilic AB diblock copolymers in which one block is **A7** *(96)*. Block copolymers with NIPAM were prepared in methanol yielding materials which were both temperature and pH-responsive. The copolymers possessed varying compositions (although the **A7** block length was kept constant at DP_n = 110); the theoretical molecular weights were in the range 15K - 25K, and the polydispersity indices were low with $M_w/M_n \leq 1.15$. As expected, these copolymers exhibited aggregation behavior which was dictated by both the solution pH and temperature; however, H-bonding interactions between the **A7** and NIPAM segments had a significant effect on the self-assembly behavior of these materials in aqueous media.

Ying and coworkers recently described the synthesis of **A7**-NIPAM block copolymers grafted from a poly(vinylidene fluoride) (PVF) substrate. (97) PVF initially was treated with O_2/O_3 introducing peroxide functionality on the PVF surface. **A7** was then polymerized from the PVF-modified surface in the presence of 1-phenylethyl dithiobenzoate in DMF at 60 °C. After purification and isolation, NIPAM was block copolymerized with the surface attached poly**A7**. The authors subsequently demonstrated that this doubly-responsive grafted membrane material exhibited both pH- and temperature-dependent permeability to aqueous solutions.

In contrast to **A7**, methacrylic acid (**A8**) has been little studied. The RAFT polymerization of **A8** was first reported by Chong *et al.* in which an AB diblock copolymer of benzyl methacrylate with **A8** was prepared using CDB in DMF *(92)*. The resulting block copolymer had an M_n of 2,400 and polydispersity index of 1.09. Unfortunately, no conversion data were presented, and given that the benzyl methacrylate macro-CTA had an experimentally determined M_n of 1,800, the final materials contained only 6 **A8** residues.

de Brouwer and coworkers *(98)* have conducted studies regarding the application of RAFT to miniemulsion syntheses. In the presence of nonionic surfactants, poly[(2-ethyl)hexyl methacrylate-*block*-(methyl methacrylate-*co*-

methacrylic acid)] copolymer was prepared by a semi-continuous procedure. The block copolymerization proceeded in a controlled fashion as evidenced by the linear evolution of molecular weight with conversion and the low final polydispersity.

Sprong et al. *(54)* described the synthesis of model alkali-soluble rheological modifiers by RAFT in which **A8** was copolymerized with methyl methacrylate in dioxane with AIBN and bis(thiocarbonyl) disulfide. In this experiment, the active RAFT agent was generated in situ. In addition to these simple random amphiphilic copolymers, statistical terpolymers and block copolymers were prepared incorporating a hydrophobic macro-comonomer with associative properties. In a follow up paper *(99),* the effect of the ethylene oxide chain length on the rheological properties was evaluated. Of the three different spacer lengths evaluated, those with 50 ethylene oxide units yielded materials which exhibited the highest viscosities in alkali solutions.

An alternative method for obtaining **A8**-containing (co)polymers is to employ protected methacrylic esters which can be readily converted to **A8** residues under facile conditions after polymerization. This is a pre-requisite strategy for **A8**-containing (co)polymers prepared by more traditional techniques such as anionic or group transfer polymerizations. A common protected methacrylic acid ester that has been studied widely in recent years is the *N*-hydroxysuccinimide ester (NHSUC) of **A8**. For example, Savariar and Thayumanavan *(100)* reported the statistical copolymerization of NIPAM and NHSUC via NMP, ATRP, and RAFT. In the case of RAFT, the polymerizations were mediated by AIBN and cyanoisopropyl dithiobenzoate. RAFT proved to be the method of choice, enabling the preparation of copolymers of varying composition in a controlled fashion.

Besides methacrylic acid, the only other α-substituted acrylic acid that has been reported to polymerize under RAFT conditions is α-ethylacrylic acid (**A9**) *(101)*. The authors reported the attempted alternating copolymerization of **A9** with maleimide (MI) in dioxane in the presence of CDB, and AIBN; however, in all instances, the process was uncontrolled with experimentally determined molecular weights significantly higher than predicted and polydispersity indices in the range 1.93 - 2.96. The lack of control was attributed to the strong self-association of **A9** in the polar solvent, coupled with a strong interaction of the imino species of MI with the $-CO_2H$ functionality of **A9**. Improved syntheses, at least at conversions < 30 %, were realized when the ethyl ester of **A9** was copolymerized with MI. In these instances, copolymers with close theoretical and experimental molecular weights and low polydispersity indices, < 1.40), were obtained.

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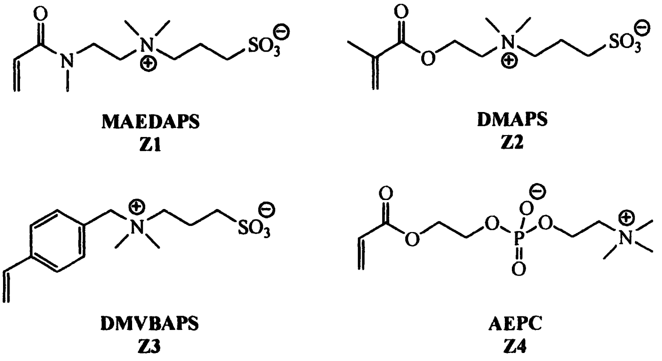
Zwitterionic (betaine) (Co)polymers via RAFT

Polymeric betaines were first reported in the 1950's. Since that time there have been a large number of reports detailing the synthesis of these highly functional (co)polymers, and most of the reports involve the conventional free radical polymerization of betaine monomers. These materials possess very interesting solution properties, such as antipolyelectrolyte behavior, *(102, 120-122)* and certain derivatives have been examined extensively in biomedical applications due to their biomimetic chemical characteristics *(103-108)*. More recently, well-defined examples have been reported by group transfer polymerization (GTP), *(70-71, 107, 109)* NMP, *(113)* and by ATRP *(79, 111-114)*. Those reported by GTP and NMP were prepared by post-polymerization modification of functional precursor (co)polymers. While this particular strategy is effective, it suffers from the potential problem of non-quantitative derivatization yielding non-ideally defined structures. ATRP does allow for the direct polymerization of betaine monomers leading to more well-defined species, but as a technique it has so far been limited to methacrylic derivatives. Several research groups have examined the application of RAFT for the synthesis of polymeric betaines. For example, Arotçaréna et al. *(110)* reported the synthesis of AB diblock copolymers of NIPAM and 3-[N-(3-methacrylamidopropyl)-N,N-dimethyl]ammoniopropane sulfonate (SPP) prepared under RAFT conditions employing benzyl dithiobenzoate as the RAFT agent. However, the block copolymers proved difficult to characterize, and no information regarding polydispersities or demonstrations of controlled behavior were presented. A more detailed evaluation of the aqueous solution properties of these copolymers was reported by Virtanen et al. *(44)*.

Subsequently, our group has demonstrated facile conditions for preparing polymeric betaines by RAFT *(57, 120-121)*. In these studies, excellent control over the molecular weight and polydispersity was observed for monomers **Z1**, **Z2**, and **Z3** (Figure 6).



MAEDAPS Z1

DMAPS Z2

DMVBAPS Z3

AEPC Z4

Figure 6. Chemical structures of zwitterionic monomers polymerized by RAFT.

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For example, Donovan and Sumerlin *(56)* reported the synthesis and aqueous solution properties of AB diblock and ABA triblock copolymers of DMA and **Z1** employing CTP, and the novel difunctional RAFT agent *N,N'*-ethylenebis[2-(thiobenzoylthio)propionamide] (TBP). These CTAs were used to prepare ω- and α,ω-dithioester end-capped polyDMA macroRAFT agents in benzene. Even though TBP and the difunctional CTA possess structurally similar R groups, significant differences in the homopolymerization kinetics were observed for these two species. Specifically, in the case of the difunctional RAFT agent, an extended inhibition period was observed versus no inhibition in the case of TBP. This difference was attributed to a higher effective local concentration of dithioester functionality early in the polymerization for the difunctional CTA. In both cases, the polyDMA homopolymers had controlled molecular weights and low polydispersity indices. The polyDMA macroCTAs were employed as macroRAFT agents for the block copolymerization with **Z1** in 0.5 M NaBr at 70 °C. These novel AB di- and ABA triblock copolymers were predicted to exhibit interesting aqueous solution properties by virtue of the tunable solubility characteristics of the **Z1** residues. In particular, polymeric betaines exhibit salt-dependent aqueous solubility with many being insoluble in water in the absence of low molecular weight electrolyte but becoming soluble at some critical concentration of added salt. Given the block nature of these copolymers, it was predicted that they would undergo reversible supramolecular self-assembly, forming star-micelles in the case of the AB diblock copolymers and flower-micelles for the triblock materials.

In addition to the sulfobetaines, the copolymerization of 2-acryloyloxyethyl phosphorylcholine (**Z4**) with both styrene and BA *has* been reported *(58-59)*. In the case of the styrene-based block copolymers, a polystyrene macroCTA was first prepared using benzyl dithiobenzoate. Block copolymers were then prepared in a DMF/methanol solvent mixture with AIBN employed as the free radical source. Two polystyrene macroCTAs of different molecular weight were prepared allowing the synthesis of a wide range of block copolymers of varying composition and molecular weight. The resulting block copolymers were generally soluble in carbon disulfide and could be cast into films to yield novel honeycomb-structured porous materials. In the case of the butyl acrylate-based block copolymers, butyl acrylate homopolymers were first prepared using 3-benzylsulfanylthiocarbonylsulfanyl propionic acid as the RAFT agent with AIBN in toluene. **Z4** was block copolymerized with the macroCTA in an ethanol/dimethylacetamide solvent mixture with AIBN. While analysis of the resulting block copolymers proved difficult, the authors demonstrated, via light scattering studies, that the AB diblock materials were capable of undergoing supramolecular self-assembly to form micelles. To date, neither carboxybetaine nor dicyanoethenenolate derivatives have been polymerized under RAFT conditions.

Summary/Conclusions

This chapter has illustrated the developments of reversible addition-fragmentation chain transfer (RAFT) polymerization for the preparation of hydrophilic, ion-containing (co)polymers either directly in aqueous media under homogeneous conditions or in organic media. This area of research continues to receive attention with new monomers and CTAs having been recently reported *(116-122)*. Thus, RAFT has evolved into a powerful tool for the synthesis of ionic polymers. A wide range of functionality can be incorporated into the monomer structure without sacrificing control of the polymerization. Thus, (co)polymers with cationic, anionic, and zwitterionic (betaine) functionality can be readily prepared under facile conditions. Of the currently available controlled polymerization techniques, RAFT has proven to be the most versatile with respect to the preparation of ion-containing (co)polymers directly in water under homogeneous conditions.

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Chapter 7

Synthesis of Polyelectrolytes via Ring Opening Metathesis Polymerization

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Examples of general synthetic approaches employed for the synthesis of polyelectrolytes via ring opening metathesis polymerization (ROMP) is described. Examples of both classical and living ROMP are highlighted.

Introduction

Polymers possessing ionic functional groups constitute a very important class of macromolecule. Such polymers include naturally occurring biomacromolecules such as polypeptides and DNA, with synthetic ionic polymers being of commercial importance as viscosifiers and soaps for example.(1) Ionic polymers can be divided into two classes, polyelectrolytes and polyzwitterions.(1) Polyelectrolytes consist of two subclasses: polycations, which are polymers with positively charge functional groups and polyanions,

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

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those materials with negatively charge functional groups. These positively or negatively charged polymers have been used commercially in biocides, enhanced oil recovery, drug delivery, coatings, personal care products, and water treatment.(2) Some common cationic and anionic polyelectrolytes are shown in Figure 1.

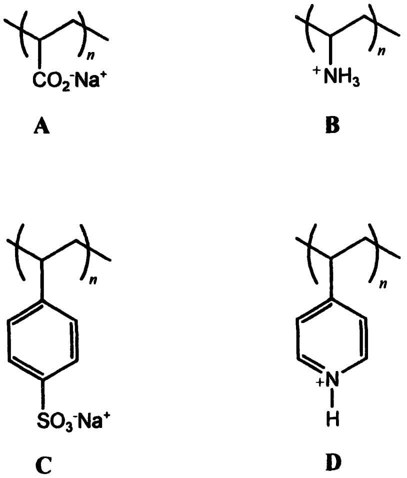

Figure 1. Example of some ionized polymers based on A) poly(acrylic acid), B) poly(vinyl amine), C) poly(styrene sulfonic acid) and D) poly(4-vinylpyridine)

Amphiphilic polyelectrolytes possess both charged and hydrophobic groups along the polymer backbone either in a statistical arrangement or a block architecture thus providing the possibility for supramolecular self-assembly into a variety of organized structures.(3)

Polyelectrolytes exhibit interesting aqueous solution properties. For example, they can undergo conformational changes or phase transitions in deionized water upon the addition of a low molecular weight electrolyte such as NaCl. In the absence of a low molecular weight electrolyte, polyelectrolytes have an extended conformation resulting in a large hydrodynamic volume. This is due to the electrostatic repulsive forces between mutually charged groups along the polymer backbone. Changes in solution pH or the addition of a low molecular weight electrolyte screens the repulsive electrostatic forces causing the polymer chain to have a compact conformation. This type of aqueous solution behavior is termed ***the polyelectrolyte effect*** in which the viscosity decreases with an increase in electrolyte concentration as shown in Figure 2.(4)

A number of polymerization techniques have been used for the synthesis of polyelectrolytes ranging from conventional free radical polymerization to controlled/"living" polymerization techniques. Ring Opening Metathesis Polymerization (ROMP) is a transition metal-mediated polymerization technique that is applicable to strained cyclic alkenes such as norbornene derivatives.(5,6) The use of well-defined, sinlge component initiators such as those based on the Schrock complex **1** (7) or Grubbs complex **2** (Figure 3) (8) makes ROMP a 'living' process. The application of such initiators allows for the synthesis of well-defined polymers with controlled molecular weights, narrow molecular weight distributions, end group functionalities, and complex macromolecular architectures. For example, in addition to ROMP's commercial utility (9), highly functionalized polymers derived from complex biological molecules such as carbohydrates (10-13), nucleic acid bases (14,15), peptides (16,17), and anti-tumor compounds (18) have been prepared via this technique.

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One novel feature that classic and 'living' ROMP provides over other polymerization techniques is the ability to prepare polymers with olefinic unsaturation along the polymer backbone. This key feature facilitates further post-polymerization chemical modification to the polymer backbone, which can generate materials with new and interesting properties. Also, variation in the double bond geometry can influence the adopted chain conformation of polyelectrolytes prepared via ROMP, thereby affecting the rheological properties in aqueous solution.(19) While there are a limited number of groups employing ROMP for the synthesis of polyelectrolytes, the preparation of these polymers does warrant discussion. Therefore, in this chapter we discuss synthetic strategies that have been employed for the preparation of polyelectrolytes under ROMP conditions.

Synthesis of Polyelectrolytes under Classical ROMP Conditions

Ill-defined (typically multicomponent) initiator systems based on transition metal salts such as $RuCl_3$, $OsCl_3$, and $MoCl_5$ were initially used for the preparation of polyelectrolytes via ROMP.(20-22) Hamilton and co-workers have synthesized three different types of polyelectrolytes including conjugated (22), amphiphilic (21), and hydrogels (19) under such conditions. This was accomplished by two synthetic approaches: 1) polymerization of an appropiate anhydride monomer followed by hydrolysis to yield the sodium salt or 2) conversion of the anhydride monomer to the diester followed by hydrolysis to yield the corresponding sodium salt,(20) Figure 4.

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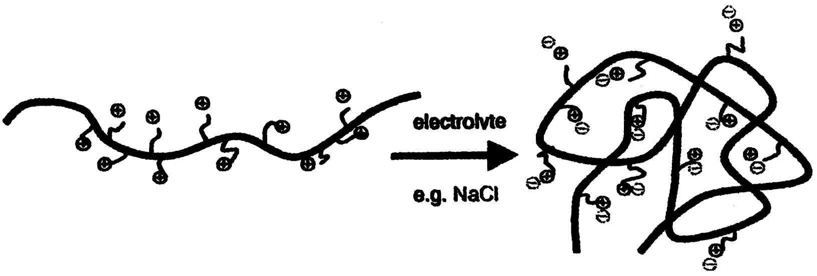
electrolyte
e.g. NaCl

Figure 2. The polyelectrolyte effect of a cationic polymer in deionized water.

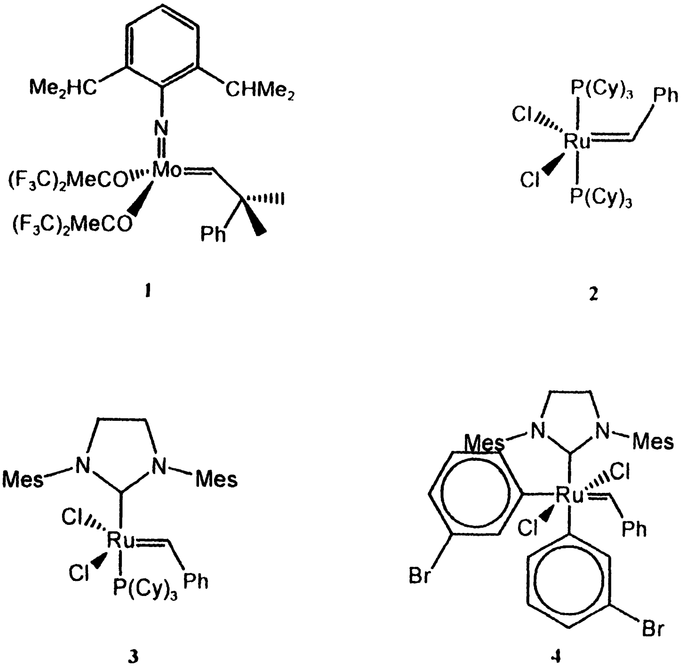
Me₂HC
CHMe₂
N
(F₃C)₂MeCO
Mo
(F₃C)₂MeCO
Ph
1
P(Cy)₃
Ph
Cl
Ru
Cl
P(Cy)₃
2
Mes
N
N
Mes
Cl
Ru
Cl
P(Cy)₃
Ph
3
Mes
N
N
Mes
Cl
Ru
Cl
Ph
Br
Br
4

Figure 2. Examples of well-defined preformed metal carbenes

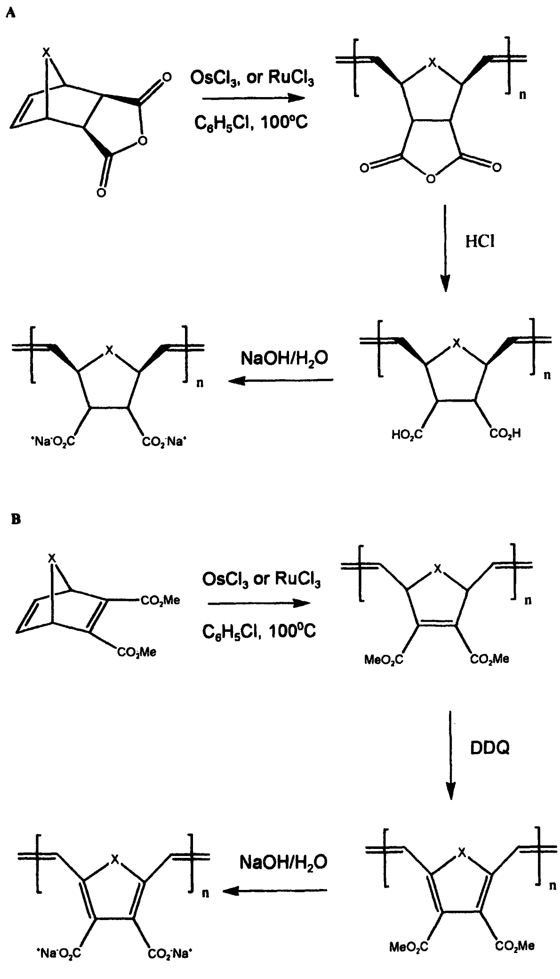
A
X
O
O
O
$OsCl_3$, or $RuCl_3$
C_6H_5Cl, 100°C
n
HCl
NaOH/H_2O
$^+Na^-O_2C$
$CO_2^-Na^+$
HO_2C
CO_2H
B
CO_2Me
$OsCl_3$ or $RuCl_3$
C_6H_5Cl, 100°C
MeO_2C
DDQ
NaOH/H_2O

Figure 4. Synthetic pathways to polyanions under ROMP conditions using transition metal salts as initiators A)hydrolysis of the anhydride polymer B)hydrolysis of the di-ester polymer C)conversion to the diacid followed by successive hydrophobic functionalization and hydrolysis, and D)conversion of the anhydride monomer to the diester, ROMP of the diester with decyl norbornene followed by hydrolysis of the diester repeat unit.

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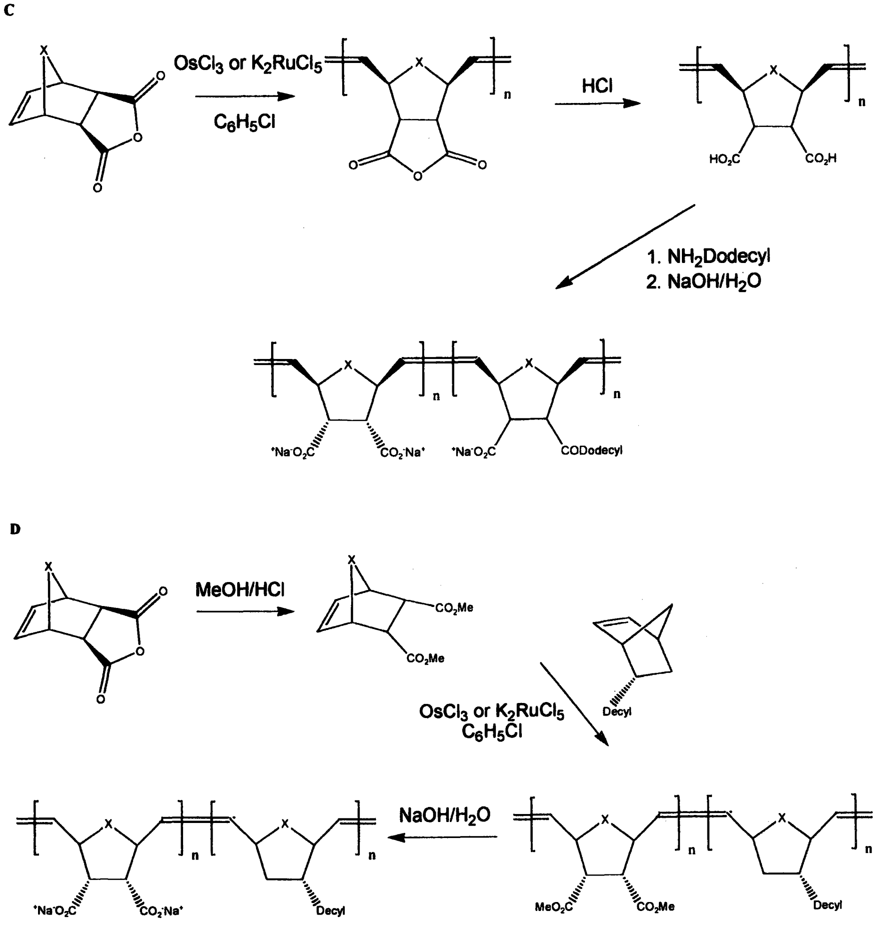
C
X
O
O
O
$OsCl_3$ or K_2RuCl_5
C_6H_5Cl
n
HCl
HO_2C
CO_2H
1. NH_2Dodecyl
2. $NaOH/H_2O$
$^+Na^-O_2C$
$CO_2^-Na^+$
CODodecyl
D
MeOH/HCl
CO_2Me
Decyl
$OsCl_3$ or K_2RuCl_5
C_6H_5Cl
$NaOH/H_2O$
MeO_2C

X = O, CH_2

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Figure 4. Continued.

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As shown above, these synthetic methods provide a route to polyelectrolytes including those with hydrophobic functionality. However, the use of ill-defined catalysts does not lead to 'living' polymerizations and thus the resulting materials are poorly defined.

Synthesis of Polyelectrolytes Under 'Living' ROMP Conditions

The ROMP of norbornene derivatives using well-defined metal carbenes, such as **1** and **2**, can proceed in the absence of undesirable side reactions and therefore can proceed in a living manner. This allows for the preparation of homopolymers and block copolymers with control over the molecular weight via changes of the monomer to catalyst ratios. Several research groups have exploited this feature for the synthesis of well-defined polyelectrolytes as well as polyelectrolyte block copolymers.

For example, Feast and co-workers reported the synthesis of poly(1,4-cyclopentenylene-5,6-ethylidene-2,3-disodium dicarboxylate)s derived from the diester shown in Figure 5 using a Schrock complex.(23)

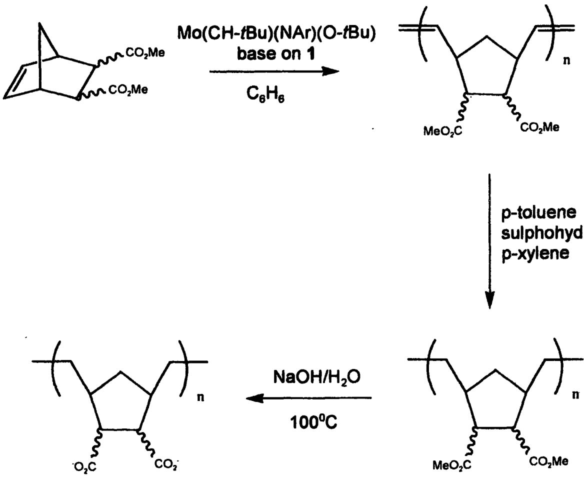

Figure 5. Living ROMP of an anionic polyelectrolyte

The resulting polydispersity indices (PDI's) ranged from 1.01 to 1.24 prior to hydrogenation and hydrolysis. However, the post-polymerization modifications led to an increase in the PDI's to as high as 1.7. Ilker and co-workers reported the synthesis of amphiphilic polymers in which the hydrophilic and hydrophobic portions were located on the same monomer.(24) Both cationic and anionic amphiphilic polymers were prepared using two different synthetic routes illustrated in Figure 6.

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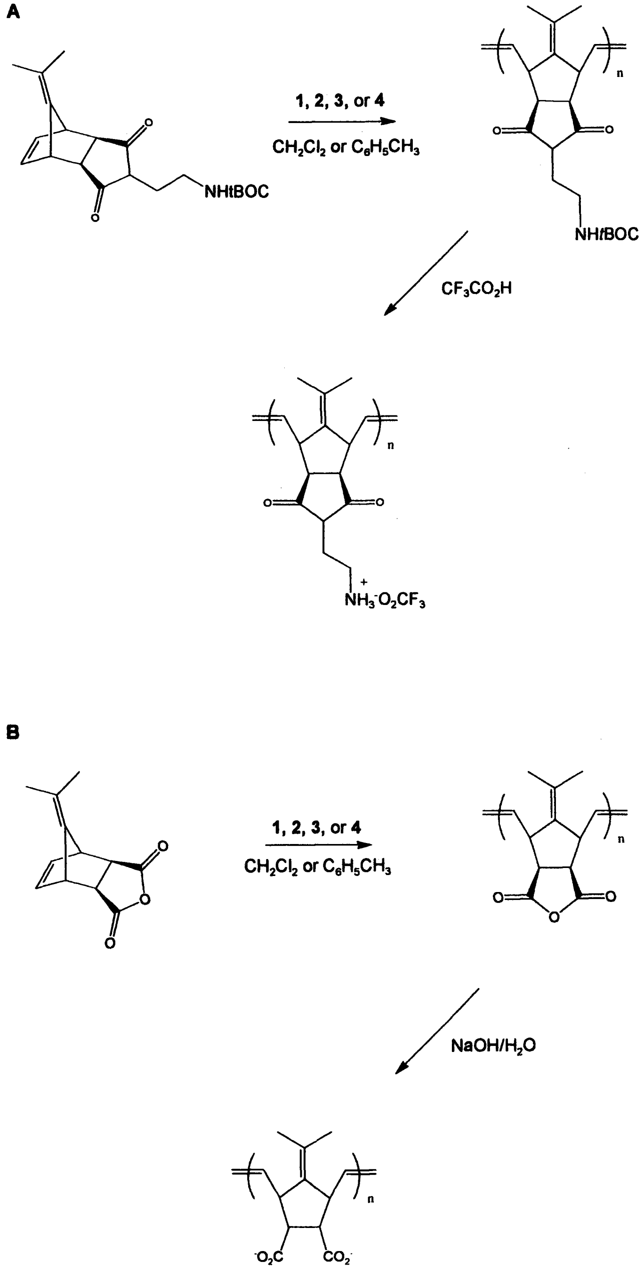
A
O
O
NHtBOC
1, 2, 3, or 4
CH_2Cl_2 or $C_6H_5CH_3$
n
O
O
NH*t*BOC
CF_3CO_2H
n
O
O
$\overset{+}{N}H_3{}^{-}O_2CF_3$
B
O
O
O
1, 2, 3, or 4
CH_2Cl_2 or $C_6H_5CH_3$
n
O
O
O
NaOH/H_2O
n
$^{-}O_2C$
$CO_2{}^{-}$

Figure 6. ***A synthetic route to amphiphilic polyelectrolytes A) cationic amphiphilic polyelectrolytes B) anionic amphiphilic polyelectrolytes***

The t-BOC protecting group on the amine monomer and the anhydride functionality resulted in a monomer possessing hydrophobic character, which allowed for controlled ROMP in organic media.

Admed and co-workers reported the synthesis of diblock copolymers of norbornene and norbornenedicarboxylic acid using **1**.(25) It had previously been reported that norbornene was not suspectible to 'living' ROMP conditions.(26) However, Admed et al. were able to polymerize the norbornene block in a living fashion by first polymerizing the norbornenedicarboxylic acid bis trimethyl silyl ester block followed by norbornene. The diblock copolymer was easily converted to the norbornenedicarboxylic acid/norbornene diblock copolymer by treatment with acetic acid and water as shown in Figure 7.

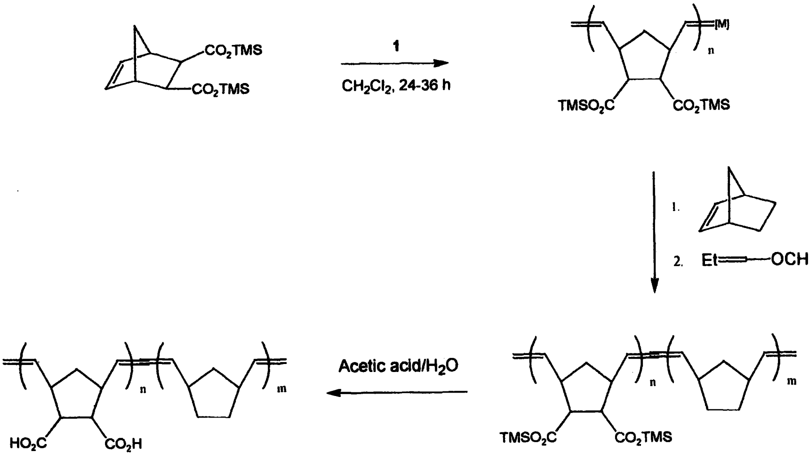

***Figure 7.** Synthesis of poly(5-norbornene-2,3-dicarboxylic acid-block-norbornene) under living ROMP conditions*

The application of protecting group chemistry allowed 'living' ROMP to be performed using **1** in organic media. It was found that an increase in the norbornenedicarboxylic acid bis trimethyl silyl ester block length led to low PDI's on the order of 1.51 to 1.05.(25)

Finally, Liaw and co-workers prepared naphthalene-lableled poly(hydrochloride-quaternized 2-norbornene-5-methylamine) under 'living' ROMP conditions using **1** as an initiator.(27) The PDI of the polymer was 1.18, which indicated the polymerization occurred in a 'living' fashion. Naphthalene labeling allowed for easy evaluation of the aqueous solution properties.

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Synthesis of Polyelectrolytes via Homogeneous Aqueous 'Living' ROMP

Aqueous ROMP of strained cyclic alkenes using group VIII transition metal salts and coordination complexes is well established.(10,28-31) These ill-defined initiators are completely water-soluble. However, the lack of a preformed metal carbene does not allow for 'living' aqueous ROMP. The first example of 'living' aqueous ROMP was reported by Grubbs and co-workers.(32) This was accomplished using previously reported well-defined water-soluble Ru-complexes **5** and **6** (33) in the presence of acid to initiate the ROMP of the water-soluble quarternary ammonium norbornene derivatives **7** and **8** as shown in Figure 8. Sequential monomer addition to poly**7** with **8** allowed for the synthesis of the corresponding block copolymer.(34)

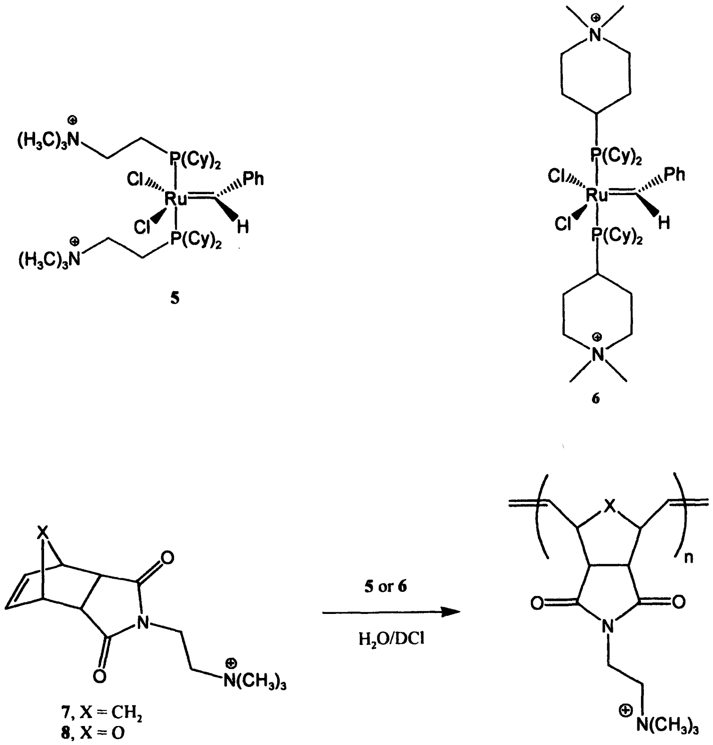

Figure 8. Homogeneous aqueous living ROMP of quarternary ammonium norbornene derivative using well-defined water-soluble Ru-complexes to yield the corresponding homopolymers.

The livingness of the polymerizations was confirmed by a comniantion of ^{1}H NMR spectroscopy and GPC experiments.

Summary/Conclusions

In short, we have highlighted some of the synthetic strategies employed for the synthesis of polyelectrolytes using classical and 'living' ROMP. While the preparation of polyelectrolytes under classical ROMP conditions is well known the advent of well-defined initiators has led to the synthesis of polyelectrolytes with complex macromolecular architectures possessing interesting aqueous solution properties. The promise homogeneous aqueous living ROMP provides will no doubt ultimately lead to the synthesis of polyelectrolytes with even more interesting aqueous solution properties and architecturally advanced water-soluble polymers for speciality applications.

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Chapter 8

Low Charge-Density Amphoteric Copolymers and Terpolymers with pH- and Salt-Responsive Behavior in Aqueous Media

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Design, synthesis, and characterization of series of model low-charge density amphoteric terpolymers containing sodium 3-acrylamido-3-methylbutanoate (NaAMB) and its valine based isomer, N-acryloyl-valine (VAL), are discussed. Stimuli-responsive aqueous solution properties are examined as a function of pH and salt concentration utilizing NMR, viscometry, and aqueous SEC-MALLS techniques.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

Extensive industrial and fundamental academic research has been directed toward the development of synthetic polyampholytes based on their potential for application in petroleum production, drag reduction, superabsorbants, water treatment, and the formulation of pharmaceuticals, cosmetics, and personal care items *(1-3)*. It has been shown that low charge density polyampholytes derived from the terpolymerization of cationic and anionic monomers with acrylamide (AM) typically have greater solubility and greater viscosifying ability than high charge density polyampholyte copolymers, and the onset of intermolecular electrostatic associations occurs at the lower polymer concentrations for low-charge-density polyampholytes *(4-11)*.

Our current research is focused on the synthesis and characterization of two categories of charged PAMs: polyelectrolytes and polyampholytes. Polyelectrolytes contain *either* anionic or cationic charges along the polymer chain, while polyampholytes contain *both* anionic and cationic moieties *(12-13)*. The solution properties (i.e. intrinsic viscosity, hydrodynamic diameter, etc.) of both polyelectrolytes and polyampholytes are governed primarily by the intra- and intermolecular electrostatic interactions that occur among the charged groups in aqueous media. In the case of polyelectrolytes, the coulombic repulsion between like charges along the polymer chain leads to a dramatic increase in the hydrodynamic volume of the polyelectrolyte coil; however, in the presence of small molecule electrolytes (e.g. salt), the coulombic repulsions are shielded, leading to a decrease in hydrodynamic size and solution viscosity.

By contrast, the coulombic forces between the positively and negatively charged repeat units of polyampholytes cause the polymer coils to have reduced hydrodynamic volumes in deionized water. Upon the addition of electrolyte to a polyampholyte solution in the dilute regime, an increase in the hydrodynamic volume of the polymer is observed due to the disruption of the intramolecular charge-charge attractions by the added electrolyte. This phenomenon is often referred to as the ***antipolyelectrolyte effect***. Although electrostatic interactions tend to dominate the solution behavior of ion-containing polymers, other effects, such as hydrogen-bonding and hydrophobic interactions, also play a critical role in determining the conformational properties. The solution behavior of amphoteric PAMs is further influenced by (co)polymer composition, monomer sequence distribution, molecular weight (MW), MW distribution, and solvent pH and ionic strength.

Previous studies in our group have shown that copolymers of AM with low mole fractions of sodium 3-acrylamido-3-methylbutanoate are exceptional viscosifiers compared to conventional anionic PAMs that contain acrylate functionalities *(14)*. Unlike the hydrolyzed PAMs, these NaAMB copolymers are able to maintain viscosity in highly saline media in the presence of divalent

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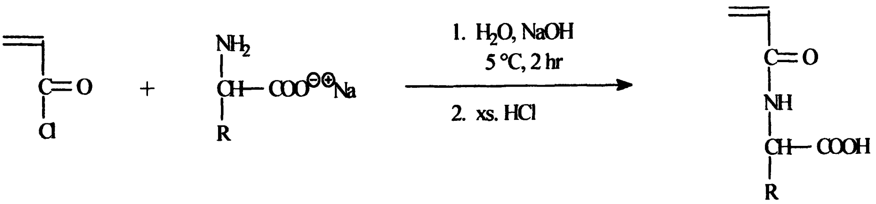
cations (e.g. Ca^{2+}, Mg^{2+}) and at elevated temperatures. Under these conditions, solutions of conventional anionic PAMs typically lose viscosity, and precipitation of the polymer may occur *(15)*.

Based on the favorable performance of NaAMB copolymers, we have prepared a variety of carboxylate-containing acrylamido monomers (Figure 1) for synthesis of low-charge density copolymers. Monomers **2**-**5** are readily synthesized from the naturally-occurring amino acids valine, leucine, aspartic acid, and glutamic acid, respectively, according to a modified literature procedure *(16)*. Reaction of the sodium salt of the amino acid with acryloyl chloride in aqueous solution, followed by acidification of the medium (Scheme 1) yields the acrylamido monomers as crystalline solids; the products are easily purified by recrystallization from water.



Scheme 1. Synthesis of acrylamido monomers bearing carboxylic acid functionalities from amino acids.

In this chapter we examine the effects of structure on dilute solution behavior of copolymers and terpolymers prepared from NaAMB **1** and the amino acid-derived monomer VAL **2**. These amphoteric isomers differ only in placement of the carboxylate functionality. However, the conformation-dependent intra- and intermolecular associations for respective polyampholyte or polyelectrolyte co- or terpolymers might be expected to be substantially altered. The conditions employed should ensure that the terpolymers possess random charge distributions, are homogeneous in composition, and do not have excessively broad MW distributions (MWDs). The terpolymers have been synthesized with the goal of creating a well-characterized series of model high MW, low charge density polyampholytes for examination of their stimuli-responsive solution behavior.

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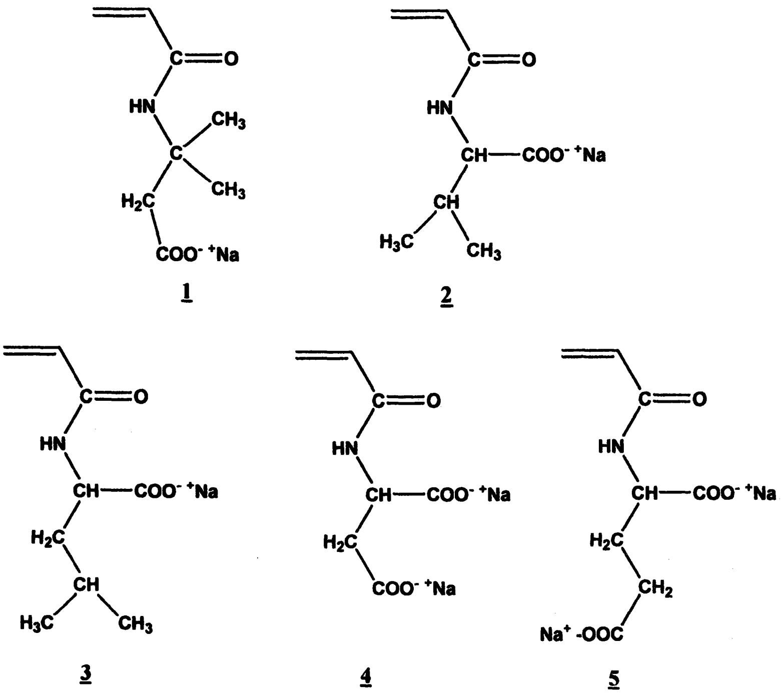

Figure 1. Carboxylate-containing acrylamido monomers employed in (co)polymers with AM.

Experimental

Materials. All chemicals were purchased from Aldrich and used as received unless otherwise noted. AM was recrystallized three times from acetone and dried *in vacuo* prior to use (m.p. = 83.5 °C). 2,2'-Azabis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) was a donation from Wako Pure Chemical Industries, Ltd. and was used as received. HCl and NaOH solutions (0.100 ± 0.005 M) were purchased from Fischer Scientific. Deionized (DI) water was obtained from a Barnstead NANOPure reverse osmosis/filtration unit (resistivity = 18.0 MΩ).

AMBATAC terpolymers. Low charge density terpolymers of NaAMB 1 with 3-(acrylamidopropyl) trimethylammonium chloride) (APTAC) and AM were prepared as previously reported (17-18). Compositional data are given in Table 1.

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Table 1. AMBATAC polyampholytes

Sample	Reaction Time (hr)	Conversion[a] (%)	AM[b] (mol %)	NaAMB[b] (mol %)	APTAC[b] (mol %)
Balanced					
AMBATAC-2.5-2.5	5.8	81	94.18 ± 0.14	3.27 ± 0.02	2.54 ± 0.14
AMBATAC-5-5	6.7	79	91.45 ± 0.31	4.27 ± 0.23	4.27 ± 0.31
AMBATAC-7.5-7.5	8.0	84	86.39 ± 0.23	6.44 ± 0.13	7.16 ± 0.15
AMBATAC-10-10	8.0	78	77.83 ± 0.69	10.74 ± 0.58	11.44 ± 0.46
Unbalanced					
AMBATAC-3-7	7.8	87	89.29 ± 0.27	3.74 ± 0.07	6.98 ± 0.28
AMBATAC-7-3	6.5	83	91.35 ± 0.69	6.32 ± 0.38	2.33 ± 0.48

[a] conversion determined gravimetrically

[b] determined *via* inverse-gated decoupled ^{13}C NMR spectroscopy

N-acryloyl valine monomer. The acrylamido monomer, acryloyl valine (VAL), was synthesized (Scheme 1) utilizing the previously mentioned procedure. A 0.5 mole portion of L-valine and 1.0 mole of sodium hydroxide were placed in a 0.5 L three-neck round bottom flask equipped with mechanical stirrer and dissolved in 200 mL of DI water. The solution was then cooled to ~5 °C. To the solution, 0.5 mole of acryloyl chloride was added slowly, due the extreme exothermic nature of the reaction, in a dropwise fashion under cooling at 0-8 °C. After complete addition of acid chloride, the solution was allowed to react for 2 hours. The mixture was then neutralized with 85 mL of concentrated HCL resulting in the formation of a white precipitate. The precipitate was collected via suction filtration, recrystallized from water, dried, and stored under N_2. The employed reaction conditions yielded > 75 % recovered product (M.P. 83 °C).

^{1}H NMR (D_2O, 25 °C, 200 MHz): CH_2CHCO 5.71 (d), CH_2CHCO 6.22 (m), HNCH(COOH)CH 4.15 (d), HNCH(COOH)CH 2.01 (m), $CHCH(CH_3)_2$ 0.98 (d).

^{13}C NMR (D_2O, 25 °C, 300 MHz): CH_2CHCO 129.0, CH_2CHCO 129.7, CH_2CHCO 169.5, HNCH(COOH)CH 58.5, HNCH(COOH)CH 176.0, HNCH(COOH)CH 29.5, $CHCH(CH_3)_2$ 18.2, 17.5.

Synthesis of AMVALTAC polyampholyte terpolymers. Low charge density terpolymers of AM, VAL, and APTAC (series will be referred to as AMVALTAC-Y-Z, where Y = mol % of VAL and Z = mol % APTAC in the monomer feed) were synthesized via conventional free radical polymerization in 0.5 M NaCl. Sodium formate (NaOOCH) was added as a chain transfer agent to control polymer MW, suppress gel effects, and avert excessive broadening of the MWD. Monomer concentration was maintained at 0.46 M, and the [monomer]:[NaOOCH] ratio was held constant at 32 to produce terpolymer samples with weight-average MWs (Mw) ranging from of $1 - 2 \times 10^6$ g/mol. The monomer-to-initiator ratio was held at 1000:1, and the reaction solution pH was adjusted to 8.0 ± 0.5 to ensure neutralization of the VAL monomer to the sodium salt form. The overall reaction is shown in Scheme 2.

To a one-liter, three-neck round bottom flask equipped with a mechanical stirrer and N_2 inlet/outlet were added DI water (750 mL) and NaCl (21.9 g, 0.375 mol). The flask was placed in a 30 °C constant temperature bath, and the contents were sparged with N_2 for 30 min. AM (21.88 g, 0.308 mol), VAL (2.93 g, 0.017 mol), APTAC (4.70 g of 75 wt % APTAC solution in water, 0.017 mol), NaOH (0.70 g, 0.017 mol), and NaOOCH (0.73 g, 0.011 mol) were added to the flask and the solution allowed to stir for 20 min under N_2 sparge. The pH of the resulting monomer solution was then adjusted to 8.0 ± 0.5 prior to initiating the polymerization. The water-soluble azo initiator VA-044 (110.5 mg, 0.377 mmol) (dissolved in 10 mL of degassed DI water) was then added to the flask by syringe. The polymerization was allowed to proceed under N_2 for 6.5 h. The stirring speed was monitored throughout the reaction to maintain a shallow vortex in the reaction medium. After reaction completion, the contents of the flask were discharged to Spectra-Por No. 4 dialysis tubing (MW cut-off =

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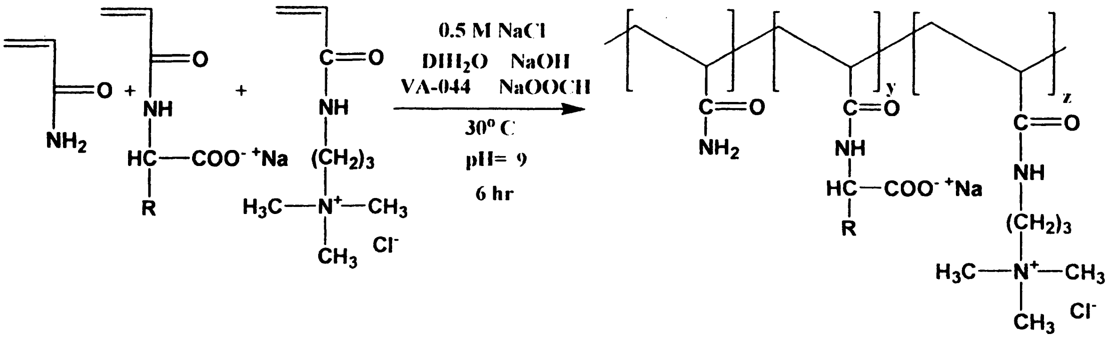
NH2
O
NH
HC
COO- +Na
R
C=O
(CH2)3
H3C
N+
CH3
Cl-
0.5 M NaCl
DIH2O NaOH
VA-044 NaOOCH
30° C
pH= 9
6 hr
y
z

Scheme 2. Synthesis of amino acid terpolymers.

12-14,000 g/mol) and dialyzed for one week, with the dialysis water being changed every 24-48 h. The pH of the dialysate was maintained ~ 7.5 to ensure the VAL repeat units remained ionized. The purified terpolymer was isolated from water via lyophilization to yield a cotton-like, white solid. Reaction conversions were determined gravimetrically.

NMR Spectroscopy. Terpolymer samples for NMR spectroscopic analysis were prepared as 5-10 wt % solutions in D_2O containing 0.5 M NaCl. All NMR experiments were performed at ambient temperature (25.0 °C ± 1.0 °C). ^1H NMR and ^{13}C NMR spectra were obtained with a Varian Mercury PLUS 300 MHz spectrometer and a Varian UNITY-INOVA 500 MHz NMR spectrometer using a standard 5 mm two-channel probe, respectively. For quantitative determination of terpolymer composition, a gated decoupled pulse sequence with a 6-7 s relaxation delay was used to suppress NOE effects. Typically, 10,000-15,000 scans were accumulated for ^{13}C spectra. All shifts were referenced automatically by the acquisition software (VNMR v6.1C) using the resonance frequency of D_2O. Incorporated error with the use of ^{13}C spectra integration for comonomer incorporation was ± 5 % of the calculated value. Data analysis was performed using MestRe-C v.2.3a spectral analysis software (Departamento de Química Orgánica, Universidad de Santiago de Compostela).

Size exclusion chromatography-multi-angle laser light scattering (SEC-MALLS). Aqueous size exclusion chromatography (SEC) was employed to determine terpolymer MW and polydispersity index (PDI). The SEC system was comprised of an Agilent 1100 series isocratic pump with a vacuum degasser, a Rheodyne 7725i manual injector with a 100 μL injection loop, two Viscogel columns (GPW_{XL}-5000 and 6000, plus a GPW_{XL} guard column, Viscotek) connected in series, a DAWN EOS 18-angle laser light scattering detector (Wyatt Technologies), and an Optilab DSP interferometric refractometer (Wyatt Technologies). Data acquisition and analysis were performed using ASTRA chromatography software (Wyatt Technologies). SEC analysis was conducted at ambient temperature (25.0 °C ± 1.0 °C). The eluent for the AMVALTAC terpolymers was 0.1 μm-filtered 0.1 M NaCl pH 7 phosphate buffer (25mM NaH_2PO_4 + 25mM Na_2HPO_4). Refractive index (RI) increments (dn/dc) of the terpolymers were determined using the refractometer in offline mode at ambient temperature. The associated error of offline dn/dc determination was typically ± 2-3 %.

Dilute solution viscometry. Stock solutions were prepared by dissolving vacuum oven-dried terpolymer samples in 0.1 μm-filtered 0.1 M NaCl pH 7 phosphate buffer (25mM NaH_2PO_4 + 25mM Na_2HPO_4). These were allowed to age 72 h while agitating gently on an orbital shaker. Subsequent dilutions of the stock solutions were allowed to age for 24 h on an orbital shaker prior to analysis. Apparent viscosities of the dilute terpolymer solutions were determined using a Contraves LS-30 low shear rheometer with a 2T cup and bob

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geometry, operating at 5.96 s^{-1} and 25.0 °C. Initial experiments at varying shear rates in the dilute regime showed the fluids to be non-shear thinning (i.e. Newtonian fluids). Therefore, the apparent viscosities determined at 5.96 s^{-1} are considered to be zero-shear apparent viscosities. Apparent viscosity measurements were repeatable with a precision of ± 1 %. Intrinsic viscosities were determined by plotting reduced viscosity versus concentration and extrapolating to zero concentration. Intrinsic viscosity determinations were repeatable to within ± 2 %.

Potentiometric titration: Potentiometric titrations were conducted at 25.0 ± 0.5 °C using an Orion 900A pH meter with a Ross Sure-Flow 8175 pH electrode. The meter was calibrated via a two-point calibration method. Terpolymer concentrations for titration were 0.50 g/dL. Minimal volume variation during the titration was achieved by adding microliter aliquots of titrant. Terpolymer solutions were adjusted to pH ~ 10 with concentrated NaOH to ensure the complete neutralization of all the carboxylic acid groups, then backtitrated using 0.1 M HCl standard solution.

Results and Discussion

AMBATAC Terpolymers. Low-charge density polyampholyte copolymers of AM containing small amounts of NaAMB and the quaternary ammonium monomer APTAC (Figure 2) were prepared *via* free-radical copolymerization in aqueous salt solution. Synthesis in saline media prevents pairing of the ionic comonomers and leads to random comonomer incorporation. Both charge balanced and unbalanced copolymers were previously prepared and characterized and are described in Table 2 *(17)*.

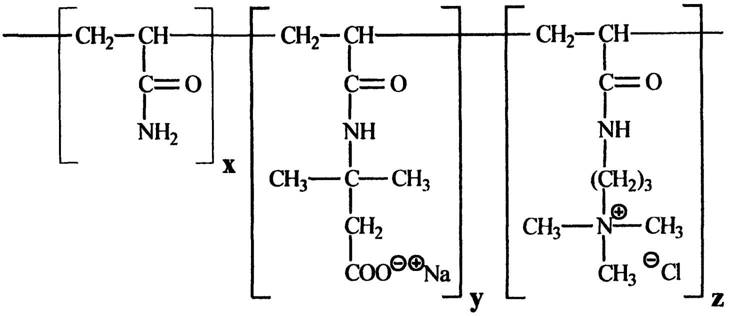

Figure 2. *Poly(acrylamide-co-sodium 3-acrylamido-3-methylbutanoate-co-3-(acrylamidopropyl)trimethylammonium chloride) (AMBATAC).*

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Table 2. AMBABTAC characterization data.

Sample	d*n*/dc[a] (mL/g)	M_w[b] (10^6 g/mol)	PDI[b]	R_g[b,c] (nm)	[η] (dL/g)[d]
Balanced					
AMBATAC-2.5-2.5	0.1729	1.38	1.63	60.9	1.78
AMBATAC-5-5	0.1737	1.51	1.51	65.7	2.15
AMBATAC-7.5-7.5	0.1738	1.56	1.72	64.6	1.45
Unbalanced					
AMBATAC-3-7	0.1754	1.34	1.83	58.8	1.62
AMBATAC-7-3	0.1765	1.53	1.80	64.5	1.96

[a] determined in 0.1 M NaCl pH 7 phosphate buffer at 25 °C ± 0.5 °C
[b] determined *via* aqueous SEC-MALLS in 0.1 M NaCl pH 7 phosphate buffer
[c] R_g = weight-average radius of gyration
[d] determined in 0.1 M NaCl pH 7 phosphate buffer at 25 °C and 5.96 s^{-1}

AMBATAC copolymers are of interest due to their pH- triggerable polyampholyte behavior *(17-18)*. At low pH, the carboxylate moieties of the NaAMB monomer units are protonated, rendering the copolymer a cationic polyelectrolyte. As solution pH is raised, the NaAMB units become ionized, and the copolymer exhibits polyampholyte behavior (e.g. the solution viscosity increases with increasing [NaCl]). Such behavior is shown in Figure 3.

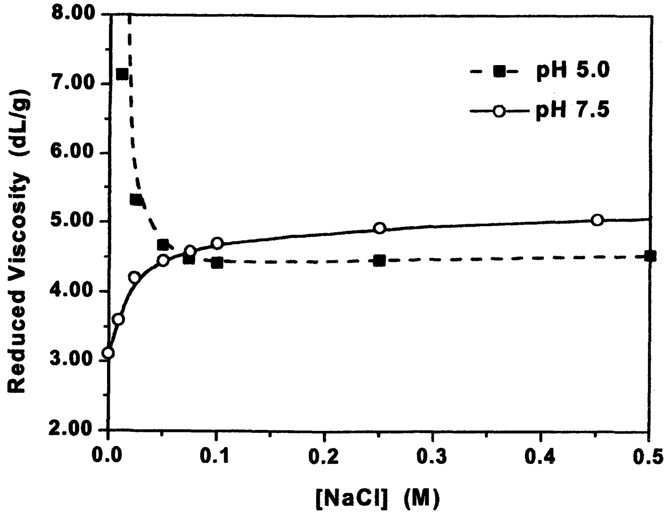

Figure 3. Reduced viscosity as a function of [NaCl] for AMBATAC-5-5 at pH = 5.0 and pH = 7.5. [Polymer] = 0.1 g/dL, T = 25 °C, shear rate = 5.96 s^{-1}.

Monomer synthesis. *N*-Acryloyl valine (VAL) was selected as an amphoteric monomer due to its pH-responsive nature, its chiral center, and its resemblance to a previously studied monomer sodium 3-acrylamido-3-methylbutanoate (stereoisomer of VAL) *(14-15,19)*. However, VAL also possesses several other features that make it potentially valuable for application in brine-tolerant viscosifiers including hydrolytic stability, steric bulk, (leading to increased polymer chain stiffness), outstanding resistance to divalent ion binding (preventing polymer phase separation in hard brines), and ease of synthesis from readily available reagents. The synthesis of VAL was accomplished in a facile manner as described in the experimental section.

Polyampholyte terpolymer synthesis. Scheme 2 depicts the reagents employed in the synthesis of the AMVALTAC polyampholyte series. Our goal was to synthesize low charge density polyampholytes with high solubility (i.e. terpolymer compositions containing a minimum of 80 % AM) and beneficial viscosifying properties as reported in previous work in similar systems *(3,20-21)*. The high levels of AM promote solubility of the AMVALTAC terpolymers, even in the absence of added electrolytes, due to the extremely hydrophilic nature of the nonionic monomer. APTAC, a non-responsive quaternary ammonium acrylamido monomer, was employed as the cationic monomer in the AMVALTAC series.

Synthesis of the AMVALTAC terpolymers was conducted under conditions expected to yield model terpolymers with homogeneous compositions, random charge distributions, and PDIs < 2.0. A 0.5 M NaCl polymerization medium was utilized to ensure random distribution of the charged groups along the terpolymer chain. This can be achieved by the screening of electronic interactions of the charged monomers by the addition of the small molecule electrolyte, thus reducing the tendency for the charged monomers to be incorporated into the terpolymer chain as alternating pairs and promoting random incorporation *(23-25)*. Sodium formate is highly trenchant in suppressing broad MWDs and controlling the MW of the free radical polymerization of acrylamido monomer systems and was utilized as a conventional chain transfer agent *(24)*. In addition to the use of sodium formate to control the MW, the polymerizations were conducted at 30 °C to minimize chain branching and hydrolysis reactions that have been reported at higher temperatures *(25-27)*.

The first column of Table 3 lists the AMVALTAC polyampholyte terpolymers synthesized for this study (AMVALTAC-Y-Z, where Y = mol % VAL and Z = mol % APTAC in the monomer feed; the remaining balance of the monomer feed is AM). The first terpolymers synthesized were those that contained essentially balanced ionic monomer content ranging from 5-15 % total ionic monomer content. In addition to the charge balanced terpolymers, two imbalanced terpolymers were also prepared, AMVALTAC-3-7 and

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Table 3. Synthesis of AMVALTAC terpolymer series.

Sample	Reaction Time (hr)	Conversion[a] (%)	AM[b] (mol %)	VAL[b] (mol %)	APTAC[b] (mol %)
Balanced					
AMVALTAC-2.5-2.5	6.5	80	94.1	3.5	2.4
AMVALTAC-5-5	6.8	81	90.7	5.0	4.3
AMVALTAC-7.5-7.5	6.25	72	85.8	6.3	7.9
Unbalanced					
AMVALTAC-3-7	6.5	75	89.8	2.9	7.3
AMVALTAC-7-3	6.5	83	89.6	6.8	3.6

[a] conversion determined gravimetrically

[b] determined *via* inverse-gated decoupled ^{13}C NMR and ^{1}H NMR spectroscopy

AMVALTAC-7-3, each bearing 10 mol % ionic co-monomers. The AMVALTAC series was designed to mirror the previously reported AMBATAC series for comparative studies *(17)*. Polymerizations were allowed to proceed for 6-7.5 hrs to obtain conversions of ~ 75%. Increasing amounts of APTAC in the monomer feed slowed the reaction slightly, and longer times were required to reach higher conversion.

Compositional analysis. Comparative integration of ^{1}H and inverse-gated decoupled ^{13}C NMR spectroscopy allow for the quantitative determination of the terpolymer compositions (Table 3). The carbonyl peak of the VAL and APTAC overlap, thus making elucidation difficult without the use of the ^{1}H NMR data. The terpolymer compositions determined via NMR spectroscopy are in good agreement with the target compositions shown in Table 1 and typically deviate less than 1.0 mol % from the target values.

SEC-MALLS and intrinsic viscosity analysis. MW, R_g, and PDI for the AMVALTAC polyampholyte terpolymer series were obtained by aqueous SEC utilizing multi-angle laser light scattering (MALLS) and refractive index detection. An aqueous, 0.1 M NaCl, phosphate buffer was employed as the SEC eluent to ensure solubility of the charge-balanced polyampholyte terpolymers and suppression of polyelectrolyte effects in the unbalanced systems. The d*n*/dc values determined offline (Table 4) were used in conjunction with MALLS detection to determine the absolute MWs of the terpolymers .

M_w, PDI, and R_g values for the AMVALTAC terpolymer series are listed in Table 3, and *M*WDs are shown in Figure 4. The M_w values of the terpolymers range from 1.2 – 1.8 x 10^6 g/mol, corresponding to *DPs* of 1.4 - 2.0 x 10^4 repeat units. The data indicate that the use of sodium formate as a chain transfer agent is effective since all AMVALTAC terpolymers exhibited unimodal MWDs with PDI values ranging from 1.5-1.6. R_g (weight-average) values ranged from 68 – 87 nm in the 0.1 M NaCl pH 7 phosphate buffer eluent, indicating that the terpolymers were of similar size.

As previously mentioned, our choice of SEC eluent was of significant importance for the examination of the relationships of R_g vs. MW and $[\eta]$ vs. MW in that the terpolymers must be as close to theta conditions as possible to ensure accurate comparisons of each relationship. Characterization by SEC-MALLS, provides an R_g value for each slice of the chromatogram enabling examination of the relationship between R_g and MW shown by Equation 1.

$$R_g = K_{Rg} \cdot M^{\rho} \qquad (1)$$

In Equation 1, R_g is the radius of gyration; M is the polymer MW, and K_{Rg} and ρ are the intercept and slope of the log-log plot of R_g vs. M, respectively. The value of ρ (slope) can be related to the macromolecular conformation of the

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Table 4. SEC-MALLS analytical data for AMVALTAC terpolymer series.

Sample	d*n*/dc[a] (mL/g)	M_w[b] (10^6 g/mol)	PDI[b]	R_g[b,c] (nm)	*DP* $\times 10^{-4}$[d]
Balanced					
AMVALTAC-2.5-2.5	0.1747	1.37	1.62	67.9	1.78
AMVALTAC-5-5	0.1752	1.80	1.52	87.3	2.15
AMVALTAC-7.5-7.5	0.1795	1.12	1.62	70.9	1.45
Unbalanced					
AMVALTAC-3-7	0.1821	1.27	1.61	76.1	1.62
AMVALTAC-7-3	0.1819	1.67	1.50	85.0	1.96

[a] determined in 0.1 M NaCl pH 7 phosphate buffer at 25 °C ± 0.5 °C

[b] determined *via* aqueous SEC-MALLS in 0.1 M NaCl pH 7 phosphate buffer

[c] R_g = weight-average radius of gyration

[d] *DP* = weight-average of polymerization, calculated from the M_w and ^{13}C and ^1H NMR

polyampholyte in solution *(28)*. The theoretical ρ-values range from 0.33 for hard spheres, 0.50 for random coils at theta conditions, 0.55-0.60 for random coils in good solvents, and 1.0 for rigid rods. The ρ-values for the entire AMVALTAC series are shown in Table 5. Examination of the data indicates that the 0.1 M NaCl pH 7 phosphate buffer is essentially a theta solvent at 25 °C.

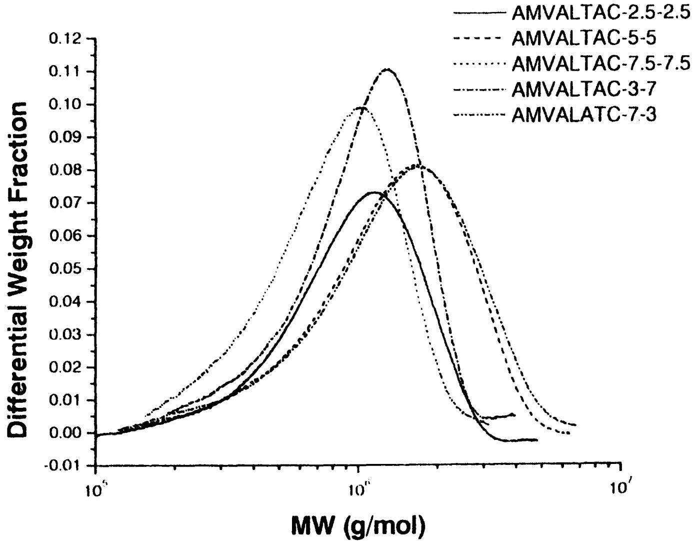

Figure 4. Molecular weight distributions of the AMVALTAC terpolymer series.

The Flory-Fox relationship (Equation 2), relates the intrinsic viscosity ([η]) of a polymer to the MW and R_g of an unperturbed coil (i.e. at or near theta conditions, where excluded volume effects are minimal).

$$[\eta] = 6^{\frac{3}{2}} \Phi_0 \frac{\left(R_g\right)^3}{M} \qquad (2)$$

From Equation 2, M is the polymer MW and Φ_0 is the Flory viscosity constant *(29-30)*. From the R_g vs. M relationship for the AMVALTAC terpolymers, it can be seen that the terpolymers do not exhibit significant excluded volume effects under the employed SEC conditions, and therefore the Flory-Fox relationship can be used to calculate the intrinsic viscosities of the terpolymers from the R_g and MW at each point on the SEC chromatogram. A range of values for the Flory constant have been reported ($1.81 - 2.87 \times 10^{23}$ mol^{-1}), but since the terpolymers investigated in this work were of high *DP* and linear chain structure, the Hearst-Tagami asymptotic value of Φ_0 for non-free-

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Table 5. Viscometric and SEC-MALLS data for [η]-*M* and R_g-*M* relationships for the AMVALTAC terpolymer series.

Sample	$[\eta]_{SEC}$[a] (dL/g)	$[\eta]$[b] (dL/g)	K_{MHS}[c] (10^3 dL/g (g/mol)$^{-a}$)	a[c]	a[d] (calculated)	K_{R_g}[e] (10^2 nm^1 (g/mol)$^{-\rho}$)	ρ[e]
Balanced							
AMVALTAC-2.5-2.5	4.1	3.8	3.59	0.47	0.50	12.5	0.51
AMVALTAC-5-5	5.2	4.4	7.75	0.46	0.47	10.6	0.49
AMVALTAC-7.5-7.5	5.3	4.5	17.5	0.42	0.41	17.9	0.47
Unbalanced							
AMVALTAC-3-7	6.1	5.4	4.0	0.59	0.55	15.1	0.53
AMVALTAC-7-3	6.0	5.3	3.2	0.53	0.51	12.2	0.51

[a] determined using Flory-Fox relationship and SEC-MALLS

[b] determined in 0.1 M NaCl pH 7 phosphate buffer at 25 °C and 5.96 s^{-1}

[c] determined *via* aqueous SEC-MALLS in 0.1 M NaCl pH 7 phosphate buffer

[d] calculated using ρ value from R_g-*M* relationship

draining, linear flexible chains of high *DP* was employed where $\Phi_0 = 2.19 \times 10^{23}$ mol^{-1} *(29)*. With the application of Equation 3, the intrinsic viscosities of the unfractionated terpolymers samples determined by SEC-MALLS analysis, $[\eta]_{SEC}$, were calculated, where $[\eta]_i$ is the intrinsic viscosity of chromatogram slice *i* in dL/g and c_i is the polymer concentration (determined via RI detection) of chromatogram slice *i* in g/dL.

$$[\eta]_{SEC} = \frac{\sum_i ([\eta]_i \cdot c_i)}{\sum_i c_i} \qquad (3)$$

The values for the $[\eta]_{SEC}$ of the AMVALTAC terpolymer series are presented in Table 4 and range from 4.10 – 6.40 dL/g. The intrinsic viscosities of these terpolymers were also measured *via* low shear dilute solution viscometry in the SEC eluent at 25 °C. These values are also listed in Table 4 and show reasonable agreement to the $[\eta]_{SEC}$.

A second relationship can be applied to the SEC-MALLS data for MW and $[\eta]$ obtained from the AMVALTAC terpolymer series. The Mark-Houwink-Sakurada relationship (Equation 4) provides a means of relating the intrinsic viscosity of a polymer coil in solution to the MW of the polymer. From a log-log plot of $[\eta]$ vs. *M*, the coefficients K_{MHS} and *a* can be determined *(31-32)*. The MHS relationship provides information similar to that of the R_g-*M* relationship regarding macromolecular properties of the terpolymers in solution.

$$[\eta] = K_{MHS} \cdot M^a \qquad (4)$$

The MHS parameters for the AMVALTAC terpolymer series are shown in Table 4. Equation 5 provides a means to relate the MHS value of *a* to the ρ value from the R_g-*M* relationship *(29)*. Table 4 provides *a* values that were calculated from the experimental ρ values that are also shown. These calculated *a* values are in agreement with the viscometrically determined *a* values from the log-log plot of $[\eta]$ vs. *M* for the AMVALTAC terpolymers.

$$a = (3 \cdot \rho) - 1 \qquad (5)$$

Potentiometric Titration. The pK_a values for the carboxylate moieties on the VAL repeat units of the AMVALTAC terpolymer series were determined by potentiometric titration of the terpolymers in DI water. The apparent pK_a values for the AMVALTAC terpolymer series are given in Table 6. A slight upward

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Table 6. pH-responsive behavior for the AMVALTAC terpolymer series.

Sample	Apparent pK_a of VAL COOH group[a]	Charge Density[b] (mol %)	Charge Asymmetry σ/N^b
Balanced			
AMVALTAC-2.5-2.5	5.29	5.90	3.65
AMVALTAC-5-5	5.61	9.30	1.13
AMVALTAC-7.5-7.5	5.83	14.2	2.61
Unbalanced			
AMVALTAC-3-7	5.60	10.2	307
AMVALTAC-7-3	5.91	10.4	193

[a] determined in DI water at 25 °C

[b] assuming complete ionization of VAL repeat units

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

shift in pK_a of the balanced terpolymers with increasing levels of VAL content is observed. This behavior is similar to that previously reported in our lab for terpolymers of AM, AMBA, and APTAC *(17)*. The same trend can be seen for the charge imbalanced terpolymers.

Charge density is typically defined as the total number of anionic and cationic groups incorporated into a given polymer, and charge asymmetry represents the degree of charge imbalance present in a polyampholyte *(33)*. Equation 6 is used to determine the charge asymmetry, σN, of a given polyampholyte. For a polyampholyte consisting of N repeat units containing a fraction of positive repeat units, f_+, and a fraction of negative repeat units, f_-, the σN is defined where $N_+ = f_+ \cdot N$ is the number of positive (cationic) repeat units and $N_- = f_- \cdot N$ is the number of negative (anionic) repeat units present in the ampholytic terpolymer. Charge densities and charge asymmetries (assuming 100% neutralization of the VAL repeat units to the carboxylate form) of the AMVALTAC terpolymers are given in Table 5. The values for the charge asymmetries of the polyampholytes change as the solution pH is lowered due to the protonation of the VAL repeat units, as the values for N_- are pH dependent.

$$\sigma N = \frac{(N_+ - N_-)^2}{N_+ + N_-} \tag{6}$$

Amphoteric Terpolymer Comparison. Comparison of the AMVALTAC and AMBATAC terpolymers proved both systems as efficient viscosifiers, although the AMBATAC series provided slightly higher [η] values. The difference in [η] may be attributed to differences in the hydrogen-bonding ability of the AMB and VAL repeat units with neighboring AM, shown in Figure 5. AMB forms a larger intramolecular hydrogen-bonding network which induces a more extended chain conformation and resultant increase in [η]. The VAL hydrogen-bonding network is smaller and less extended. Although the size of the intramolecular interactions varies slightly, it is expected that the AMVALTAC terpolymers will exhibit similar resistance to divalent ion-binding by the creation of intramolecular sites along the polymer backbone that can chelate Ca^{2+} ions (i.e. between the VAL carboxylate group and a neighboring AM carbonyl group), preventing intermolecular crosslinking of the copolymer by Ca^{2+}.

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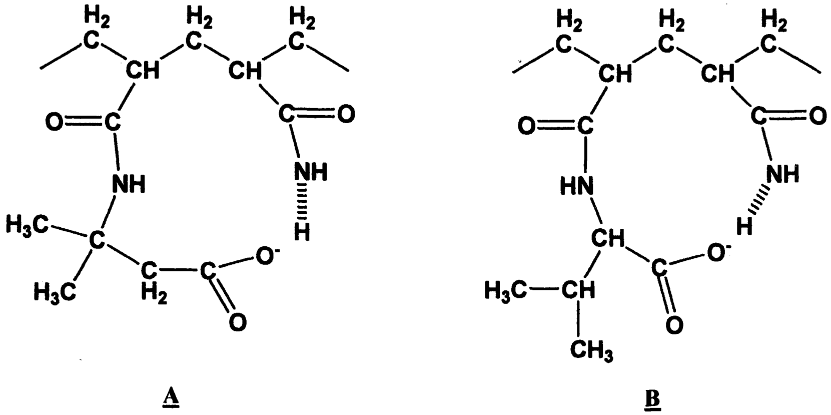

Figure 5. Postulated structures of intramolecular hydrogen-bonding between neighboring AMB/AM (A) and VAL/AM (B) repeat units in low charge density terpolymers.

Potentiometric titration also indicates slight differences in pK_a values for the amphoteric terpolymers. The AMVALTAC series possess higher pK_a values than the respective AMBATAC series. This is attributed to the different stereo- and electronic effects governing the ionization of the carboxylate functionalities of the AMB and VAL repeat units.

Conclusions

A series of low charge density model polyampholyte terpolymers composed of AM, VAL, and APTAC (AMVALTAC) were synthesized *via* conventional free radical polymerization in aqueous media for comparison to previously synthesized AMBATAC terpolymers . The reaction conditions were selected to yield terpolymers with random charge distributions, homogeneous compositions, and well-defined MW and MWDs. Compositional analysis by ^1H and ^{13}C NMR revealed agreement between monomer feed compositions and final terpolymer compositions. The AMVALTAC terpolymers were characterized extensively via SEC-MALLS analysis in 0.1 M NaCl pH 7 phosphate buffer at 25 °C. SEC-MALLS analysis showed that the use of NaOOCH as a conventional chain

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transfer agent allowed control of terpolymer MW and suppressed excessively broad MWDs. Such polymerization characteristics are of importance in developing a terploymer series that will consist of polymers within the same range of MWs and MWDs for accurate studies of macromolecular structure and solution properties. Intrinsic viscosities determined by SEC-MALLS were found to agree with intrinsic viscosities measured *via* dilute solution viscometry. The data from SEC-MALLS experiments allowed for the comparison of radius of gyration-MW (R_g-M) relationships and the Mark-Houwink-Sakurada intrinsic viscosity-MW ($[\eta]$-M) relationships for terpolymers and provided information regarding the dependence of macromolecular conformation and goodness of solvent on terpolymer composition. The R_g-M and $[\eta]$-M relationships indicated little or no excluded volume effects under SEC conditions, as expected under near theta conditions. Higher $[\eta]$ values were observed for the AMBATAC terpolymers as compared to the AMVALTAC series and may be attributed to differences in hydrogen-bonding properties of the AMB repeat unit versus the VAL repeat unit with neighboring AM. Potentiometric titration studies showed that the apparent pK_a values of the charge-balanced AMVALTAC terpolymers increased with increasing levels of VAL content in the terpolymer. The pK_a values of the AMVALTAC terpolymers were higher than their AMBATAC counterparts.

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Chapter 9

Applications of Polyelectrolytes in Aqueous Media

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This article concentrates on a few important aspects of the applications of polyelectrolytes in aqueous media. We'll discuss the behaviors and features of polyelectrolytes that make them useful in industrial applications, and the characteristics of polyelectrolytes that are important as descriptors in structure-performance correlations, especially those characteristics that are special to polyelectrolytes as compared to other polymers. Structure-performance correlations based on the physical and chemical phenomena underlying an application, coupled with metrics for both the phenomena and the polyelectrolytes allow us to bridge the intellectual gap between fundamentals and applications in complex systems. These correlations then constitute a knowledge base from which one may design solutions to existing problems, rationalize observations, diagnose upsets in existing processes, and invent novel technologies.

In Polyelectrolytes and Polyzwitterions; Lowe, A., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2006.

Phenomena Underlying Polyelectrolyte Applications

There are four major phenomena with respect to polyelectrolytes that underpin most of the useful behavior derived from their use. These phenomena are shown in the figure below, along with associated concepts and processes.

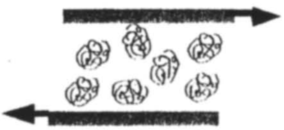
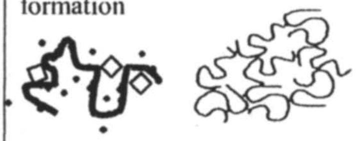
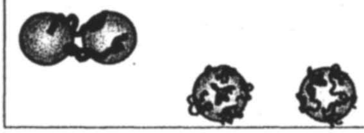
Phenomenon	Underlying Concepts & Processes
Hydrophilicity 	Solvation (dissolution; swelling; osmosis) Competition for water (other solution species)
Rheology Modification 	Chain dimensions (coil volume) Segment-solvent interactions Chain-chain interactions (entanglement and overlap) Hydrodynamics Flow kinematics (shear and elongation)
Complexation/Network formation 	Chain-chain interactions (entanglement and crosslinks) Percolation threshold Binding constants Competitive binding
Colloid stability 	Adsorption Modification of surface charge density Bridging Depletion

Figure 1. Phenomena underlying polyelectrolyte applications.

The inherent nature of polyelectrolytes to interact strongly with water is often taken for granted. The phase behavior of all other components in aqueous systems will be subject to the strong competition of ionized groups in the polyelectrolyte for water. Copolymerization of nonionic monomers with ionogenic monomers is one way to moderate this behavior in order to tune the thermodynamics of the system for a particular purpose; e.g. to drive the polyelectrolyte to a solid-liquid interface by virtue of arranging the system to approach a phase boundary. This accumulation at the solid-liquid interface is similar to the the greater surface activity seen as the conditions for phase separation are approached in surfactant systems, known as the Ross-Nishioka

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effect (*1*). Strong interaction with water also means that the entropy gained by releasing bound water should not be neglected when either designing or rationalizing a process involving polyelectrolytes.

Rheology modification of the medium occurs at all levels of polymer concentration. Polymer size in solution is a function of the chemistry of the polymer, the degree of polymerization, linkage pattern of the monomer units, and the interactions with other species in solution. The forces that result in a macromolecule occupying a certain average volume are both intrinsic (e.g. segment-segment and segment-solvent) and extrinsic (e.g. hydrodynamic and kinematic). These interactions are also important in concentrated polymer solutions, but having a different emphasis than in dilute solution.

The ability of polyelectrolytes to interact with multiple entities (other chains, solution species, surfaces, etc.) in a cooperative fashion accounts for some of their useful properties. These include complexation and network formation. Cooperativity in such interactions allows for the kind of dramatic outcomes that are the hallmark of critical phenomena, such as gelation.

Because of the combined attributes of multi-site interaction and potentially strong Coulombic interactions with other species (including water), polyelectrolytes can be useful in manipulating colloid stability. Polyelectrolyte adsorption is often an ion exchange process in which some of the ionic species are frustrated in their attempt to interact with surface species, due to their connectivity in the polymer chain. This may lead to locally uncompensated regions of charge that may drive either stabilization or destabilization.

Examples of applications in various industries that illustrate the phenomena described above are compiled in the following table.

Insightful quantitative theories based on observations of well controlled model systems give one an excellent starting point for understanding these sub-processes, and even the overall process. Theories allow us, in many cases, to organize observational data into structure-performance correlations. However, practical systems of commercial importance often present such a complex diversity of substrate compositions and environmental conditions that one is tempted to utilize only the broadest of principles derived from the theories and to forgo quantitative predictions. Still, making adequate progress towards optimizing the use of a polyelectrolyte can be made if one is thorough in considering all aspects of the application process. When actual behavior does not seem to be consistent with expected behavior, oftentimes some key element in the causal chain of sub-processes has been overlooked. This can be an opportunity for process improvement and possibly novel technology.

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Table I. Polyelectrolyte Applications Related to Key Phenomena

Application	*Example (Industry)*
Hydrophilicity	
Absorbency	Water absorption (Diapers, Agriculture)
Osmotic Control	Fluid loss control (Oil) Phase separation (Pharmaceutical)
Rheology Modification	
Oil Recovery	Mobility control (Oil)
Fluid Transfer	Drag reduction (Oil, Firefighting, Irrigation)
Power Transfer	Water-based hydraulic fluid
Thickening	Rheology control (Textiles, Paints, Adhesives, Coatings)
Complexation / Network Formation	
Sequestration	Metal ion complexation (Water Treatment, Detergent)
Oil Recovery	Profile modification (Oil)
Soil Amendment	Soil stabilization (Civil Engineering) Soil conditioning (Agriculture)
Film Formation	Coating (Cosmetic, Pharmaceutical) Antistatic coating (Coatings) Membranes (Separation) Polyelectrolyte multilayers
Adhesion/Binder	Adhesives (Dental) Cement additive (Construction) Cell fixation (Biotech)
Colloid Stability	
Flocculation	Solids recovery (Mining) Waste removal (Sewage, Industrial) Water clarification (General) Paint detackification (Automotive) Retention aid (Paper) Drainage aid (Paper)
Dispersing	Drilling muds (Oil) Pigment dispersal (Paints, Coatings) Antiscalants (Boilers/Coolers, Mining, Sugar, Textile) Anti-redeposition (Detergent)
Phase Separation	Protein isolation (Pharmaceutical) Demulsification (Oil) Aqueous dispersion polymers (Chemical)
Crystal Growth Modification	Gas hydrate inhibition (Oil)

Polyelectrolyte Properties

The properties of polyelectrolytes are more than just a superposition of the properties of neutral polymer chains and those of simple electrolytes, as the roots of the word might suggest (2). This fact is important to keep in mind when seeking appropriate descriptors to employ in structure-performance correlations. A complete description of isolated neutral chains would include the concepts of constitutive repeat units, connectivity, chain architecture (e.g. random, blocky, etc.), linkage pattern (topology, branching), spatial arrangement (coil, globular) and extent, as well as short- and long-range interactions amongst the segments. Measurements of parameters related to these descriptive features in virtually any real ensemble of chains would result in statistically distributed quantities. A further description of the neutral chains in a solvent and in the presence of other chains would require adding the concepts of solvent-segment interactions, hydrodynamics, entanglements and networks. The presence of interfaces and other solutes would necessitate adding the concepts of phase separation, complexation, multi-site adsorption, and chain conformations at surfaces (loops, tails and trains). Concepts related to the electrolyte character of the ionogenic groups that are part of the chain must also be considered. These include ionization, ion exchange, pH-dependent polyion charge (for weak polyacids or polybases), intra-chain expansion due to charge repulsion (polyelectrolyte effect), transport in an electric field, and a host of concepts surrounding the behavior of counterions (charge screening, counterion condensation, specific binding) and co-ions.

The properties of polyelectrolytes are greatly influenced by other species and forces in their environment. Thus, the behaviors of charged chains are significantly affected by water chemistry (pH, counterions, co-ions, co-solvents, dissolved gases), other soluble species (surfactants, polymers), insoluble species and interfaces, external forces (viscous, electric, centrifugal, acoustic), and forces intrinsic to the components of the system (electrostatic, osmotic, hydrodynamic).

The ionic character of polyelectrolytes may be largely understood in terms of the propensity of ionogenic groups in the chain to ionize in an aqueous environment, and the interplay between the resulting fixed charges on the polyion and the attendant counterions. The Coulombic repulsions between intra-polyion charges that drive coil expansion are mitigated by the presence of counterions, both mobile and condensed on the chain. Such interplay results in polyelectrolyte solution properties that are functions of the concentration and valency of the ionogenic groups of the polyion and of the counterions. One example is the reduction of both the intrinsic viscosity (hydrodynamic volume per macromolecule mass) and the mean square radius (R_g) of a polyelectrolyte as the salt concentration is increased (3).

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Low-molecular-weight solutes can affect the properties of a polyelectrolyte in solution in other ways as well. This may be due to preferential interactions with the polyion itself, or with the water. Preferential interactions of solutes may be classified into four groups (4).

- Polyelectrolyte effects: These include counterion condensation by which the effective charge on the polyion is reduced. These effects are seen at low to moderate salt concentrations, and only the valence of the ions is important – other aspects of the chemical nature of the salt are unimportant. For example, calculations by Record, et al (4) of a DNA chain (Manning parameter, $\xi = 4.2$) in a 1 mM solution of a 1:1 electrolyte predicted the counterion concentration near (within several hydration layers of) the polyion to be ~ 1 M, and the co-ion concentration to be ~ 1 μM; a range of 6 orders of magnitude.
- Hofmeister effects: These specific ion effects manifest as differences in the properties of ions at the same ionic strength in aqueous solutions. These effects are seen at moderate to high salt concentrations and depend on the chemical nature of the salt, especially the co-ion. Changes in the structure of water are implicated here.
- Osmotic effect: This effect governs the distribution of water in a system and is attributed to changes in the activity of the water due to the presence of the salt at moderate to high concentrations (typically > 0.1 M). Such a thermodynamic effect may result in less water available for hydrating the polyion.
- Non-Coulombic binding: Acid-base (including hydrogen bonding) and hydrophobic interactions between the solute and polyion fall into this category.

When the polyelectrolyte is comprised of ionogenic groups consisting of either weak acids or bases (e.g. acrylic acid, or 2-(acryloyloxy)ethyl dimethylamine), the effective charge on the polyion will be a function of both the extent of neutralization and the salt concentration. Thus the apparent dissociation constants are ionization-dependent and salt-dependent (5, 6). The ease of protonation or deprotonation will depend on the local charge density of the chain, and the extent to which it is screened. For example, the apparent pK_a of poly(acrylic acid) may vary more than 2 units over the full titration curve (5). The close proximity of other charged species to the polyion, such as self-assembled aggregates of surface-active species, colloids, or solid-liquid interfaces, will affect the state of charge on the polyion. The entire collection of charged species must be included in a self-consistent manner when modeling polyelectrolyte behavior, or taken into account when rationalizing response in an application.

Assuming that progress in developing a technology is well served by understanding the key factors that influence its success; we are motivated to construct structure-performance relationships that capture this understanding. The collection of properties most useful as descriptors in constructing structure-performance relationships fall into several classes. Those properties that are intrinsic to the polyelectrolyte include molecular weight, charge type and amount, chain architecture, chain topology and chemical composition. Properties related to the polyelectrolyte being in solution include molecular size, actual charge density, composition of the ion atmosphere, chain flexibility, extent of entanglements, the relative strengths of segment-segment, segment-solvent and solvent-solvent interactions, and the chemical and physical stability of the polyelectrolyte. In order to complete the picture one needs to understand the physics of the processes involved in the application, since elements of the system (constituents and force fields) may interact with the polyelectrolyte.

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Solid-Liquid Separations

We will use the example of polyelectrolyte-assisted solid-liquid separations to illustrate some features of developing a more refined understanding of applications in complex, but quite common systems. Many applications involve multiple and interacting parameters, as the following figure depicting the variables that may affect a solid-liquid separation suggests.

The basis for each of the solution physical-chemical features described in the section above involves an interaction between the polyelectrolyte and either soluble species or discrete phases, often colloidal in nature. Designing or choosing the appropriate polyelectrolyte for an application is made easier by having an understanding of both the physics of the underlying processes in an application, and how the various components of the medium influence the physical and chemical state of the polyelectrolyte and the substrate. From this perspective one can adjust the interactions of the polyelectrolyte within the context of the entire system to produce the desired result. For example, solid-liquid separations of colloidal dispersions using polyelectrolytes can be thought of as comprising several sub-processes: polymer dissolution, transport to the solid-liquid interface, adsorption, particle-particle collisions, bridging and/or colloid destabilization, growth and fracture of aggregates, sedimentation and dewatering. The figure shown below illustrates these sub-processes in a particular polyelectrolyte-assisted flocculation, which is part of a solid-liquid separation process. Approximate time scales for the sub-processes are given for the case of orthokinetically controlled collisions (mean shear rate of 1000 s^{-1}) between 2-micron bacterial particles in a suspension (1 wt% dry), which is being flocculated with 100 ppm of a cationic polyelectrolyte ($M_w = 10^7$; mean square radius = $R_g = 0.2$ microns; hydrodynamic diameter = $D_H = 0.22$ microns; ionic strength = 10 mM).

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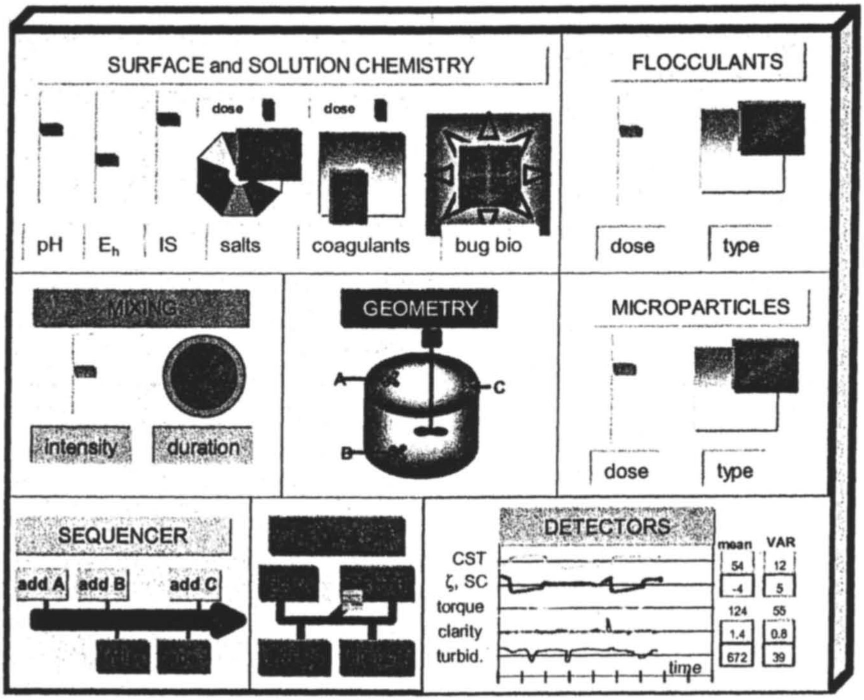
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C
MICROPARTICLES
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add A
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add C
DETECTORS
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ζ, SC
torque
clarity
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672
39

Figure 2. Tailoring Solid-Liquid Separations

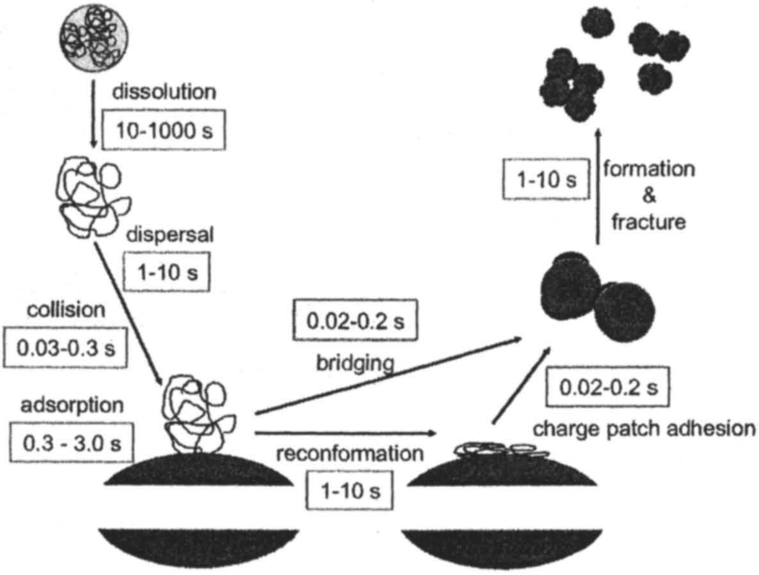
dissolution
10-1000 s
dispersal
1-10 s
collision
0.03-0.3 s
adsorption
0.3 - 3.0 s
0.02-0.2 s
bridging
reconformation
1-10 s
0.02-0.2 s
charge patch adhesion
1-10 s
formation
&
fracture

Figure 3. Polyelectrolyte-Assisted Flocculation Sub-processes.

The time scales in the above figure were estimated as follows. Practical dissolution times for high-molecular weight (M > 10^6) polyelectrolytes range from less than 1 minute to tens of minutes depending on the original form of the polymer (aqueous dispersion, inverse emulsion, dry powder, etc.). A dispersal time of 6 sec was calculated from the relationships given by Spicer et al (7) for circulation time in a square beaker with a volume of 200 cm^3, an impeller diameter of 10 cm, ann an agitator speed of 2.5 rpm (average shear rate = 1000 sec^{-1}). The time between coil-particle collisions was estimated from relationships given by Hogg (8) using the coil and particle size parameters given above. The range of adsorption times is based on collision efficiencies ranging from 1 to 0.1. Adsorbed polymer coil reconformation times were estimated based on measurements by Adachi and Wada (9). Bridging and charge patch adhesion times were estimated from collision rates between a polymer decorated particle and a bare particle using the same relationships as above. The time for macroscopic floc formation and rupture were approximated as the polymer dispersal time since all other sub-processes were faster.

These sub-processes operate with overlapping time scales and are connected in a causal chain. This means that there are a set of necessary pre-requisite conditions that must be satisfied before the collection of sub-process can yield the desired result (e.g. the polymer must be dissolved before it can successfully adsorb onto a particulate surface and thereby act as a bridging agent when a second particle comes within range). A successful application strategy involves concomitantly satisfying the pre-requisite conditions given the constraints of the physical system (e.g. water chemistry, mixing profile, contact time, etc.) and the commercial system (e.g. cost-performance ratio). In other words, it is necessary to maintain a consideration of the entire process and relevant parameters when optimizing polymer use in an application.

In the case of solid-liquid separations involving aggregation via a polyelectrolyte, some attention must be paid to the properties of the flocs produced, since these need to be matched to the particular dewatering device or scheme (10). For example, while large dense flocs may be good for sedimenting, small dense flocs are usually better for consolidating; large porous flocs are typically good for dewatering by drainage, however either the mechanical strength of the flocs must be able to withstand the breakage forces, or the broken flocs must readily reform before the dewatering phase.

Some considerations in tailoring the flocculation process, which typify knowledge gained from working with commercially relevant systems and their connection to the sub-processes mentioned above, are listed below.

- Pre-coagulation followed by flocculation: Particles must be destabilized before flocculation. Pre-coagulation usually results in small weak aggregates that are more amenable to flocculation by a high-molecular weight polymer (11). Examples of coagulants used in this regard include low-molecular

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weight polymeric coagulants (e.g. polyamines or poly(diallyldimethylammonium chloride)), organic colloids (e.g. melamine-formaldehyde condensation products), and salts of hydrolyzable metal ions (Al^{+3}, Fe^{+3}). The latter may form oligomeric/polymeric species in solution, or may be added as pre-formed oligomers.

- Dual polymer systems: This includes a subset of the previous category, wherein low- and high-molecular weight organic polymers are employed. When oppositely charged polymers are used they are most commonly employed sequentially (12). In that case the low-molecular weight polymer is most often added first and serves to create regions of high charge density on most of the particle surfaces; even when the original distribution of surface charge densities may have been heterogeneous. This allows for a more efficient functioning of the high-molecular weight flocculation subsequently added. Naturally occurring biopolymers, exogenous to the cells in bio-sludges (13), may act as one of the partners in such a dual polymer system. Also, there are instances where both the low- and high-molecular weight polymers have the same charge (14, 15), and where oppositely charged polymers are added simultaneously with good results.
- Bridging ions: Multivalent counterions in solution may act as transient junction sites between a polyelectrolyte and a surface of the same charge as the polyelectrolyte. For example, somewhat counter intuitively, anionic polyelectrolytes may be used in the flocculation of negatively charged clays in coal beneficiation if the right amount of Ca^{+2} is present in solution.
- Non-electrostatic interactions: There are a number of other attractive interactions that may cause the adsorption of a polyelectrolyte at a solid-liquid interface. These include acid-base (e.g. H-bonding), complexation (e.g. ligand formation resulting in chemisorption) and hydrophobic interactions. These mechanisms are particularly useful in high ionic strength media, or when the pH of the medium may pass through a range that leaves both the surface and the polymer with the same charge. An example of adsorption based on complexation is the use of polymeric flocculants containing hydroxamic acid functional groups that bind to the surfaces of iron oxide particles in the high ionic strength media found in the Bayer process, in which bauxite ore is digested in hot caustic for the purpose of separating out aluminum species that are subsequently recovered as aluminum trihydrate. These polymers make excellent red mud flocculants.
- Polymer topology: The linkage pattern of polymer chains can make a substantial difference in their efficacy as a flocculant in some cases. For example, cationic polyelectrolytes having modest numbers of long chain branches, such that the polymers are still soluble, perform better as flocculants in waste activated sludges that are dewatered in centrifuges (16).

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Maximizing Polymer Use Potential

Inefficiencies in the use of polyelectrolytes may occur for reasons other than a poor choice of chemistry (e.g. no driving force for adsorption) or a poor choice of physical properties (e.g. wrong molecular weight). Several other considerations that may help in optimizing polymer use are discussed below.

Polyelectrolytes are most often used in a solubilized state in the applications discussed above. Thus completeness of dissolution is usually important. Limitations on the time allotted for the dissolution step in a process may result in incomplete dissolution of the polymer, and hence a reduced effectiveness. The rate of dissolution is impacted by water chemistry, temperature, agitation scheme, and product form. Commercial polyelectrolytes are offered in the form of dry powders, gels, inverse lattices, solutions, or aqueous dispersions (phase separated aqueous droplets containing a high-molecular weight polymer in an aqueous continuous phase). Each one of the forms requires a somewhat different dissolution strategy. For example, dry powders must be sufficiently wetted before they can swell and eventually dissolve. On the laboratory scale this may be accomplished by using a small amount of an alcohol. However, on a large scale this is less practical, and the problem of adequate wetting may be addressed by a proper choice of mixing equipment.

Inverse lattices, in which the discontinuous phase comprises a high concentration aqueous polymer solution and the continuous phase is oil, must undergo the additional step of inverting (breaking) the polymer-containing droplet, before swelling and dissolution can occur. That is, the oil must be displaced from the surface of the polymer droplet so that water may contact the polymer-containing particle. Often this requires the presence of an inverting surfactant (e.g. a high HLB surfactant) to cause dewetting (de-oiling) of the dispersed droplets and emulsification of the oil phase into the dilution water. In such a case, not only is the effect of the water chemistry and other variables quoted above important for the intrinsic dissolution rate of the polymer, but the effects of those same variables on the inversion process may also be critical. This often comes down to the effects of these variables on the phase behavior of the inverting surfactant.

Completeness of dissolution is often gauged from the rheology of the dissolving composition, using either quantitative or qualitative metrics.

Once the polymer is completely dissolved one usually needs to maintain both its chemical and physical integrity, at least for the lifetime of that portion of the application process in which it must be active. Chemical alteration of the ionogenic functional group content can change the charge of the polyion, which may impact its efficacy. For example, ester linkages are prone to hydrolysis or

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they may imidize (17) if there are neighboring amide groups. If these groups are between the main chain and the ionogenic species, the result may be a loss of the original ionogenicity, and/or the generation of an anionic carboxylate group. If the original ionogenic groups were cationic, then the resulting amphoteric macromolecule could have different properties compared to the original. Thus the pH and temperature of the polymer dissolution water and the treated medium can be critical factors in maintaining the greatest efficacy of the polyelectrolyte. The use of buffers may be warranted, or the use of a functional group less prone to hydrolysis (e.g. amide) may be necessary.

More aggressive chemical degradation occurs due to free radicals present in solution. Such an attack may result in cleavage of the main polymer chain, thereby significantly reducing the molecular weight. For example, auto-oxidation of Fe^{+2} results in free radicals (18) that can cause such degradation of vinyl backbone polymers. The ambient concentration of oxygen in water exposed to air is usually enough to cause this auto-oxidation, which is exacerbated by high temperatures. The use of oxygen or free radical scavengers or the removal of the oxidizable species may be used to control this process.

Macromolecular weight degradation may also occur due to mechanical stress in the chain of sufficient magnitude to break covalent. Elongational stress is more effective than shear stress at producing this irreversible fracture. Turbulent mixing and flow through constrictions can create enough elongational stress in the polymer chain to cause such a result. Thus care in controlling the kinematic history of the polymer chains can be important. Avoiding flow through throttled valves is one example.

In addition to maintaining polymer integrity, the flow history of the polymer and substrate may also be important with respect to producing the best floc structure for the dewatering method chosen. Usually one has to strike a balance between dispersal of the coagulant/flocculant and destruction of the aggregates. Uniformity of the dispersal will depend on the relative viscosities of the fluids being mixed (flocculant and substrate), kinematics of the mixing device, and history of the mixing (sequence, duration, and intensity). For example, it is often best to mix a coagulant/flocculant with the substrate intensely for a short period of time, and then allow for a period of moderate mixing, or even quiescence, to encourage full floc development. In processes with fixed kinematics one can sometimes judiciously choose the point of reagent addition in order to satisfy the above requirements. Optimizing multi-component reagent systems also requires a consideration of sequencing the addition of the individual reagents. Even in the case of a single reagent system, dividing the reagent addition may produce benefits (19).

Structure-Performance Correlations

Refining our understanding of the interplay between polyelectrolyte, solution and substrate properties, and the physics of the processes underlying an application can proceed via the development of structure-performance correlations, wherein the effects of intrinsic macromolecular parameters on application results are quantified. An example in which the use of topologically nonlinear cationic polymers improved the flocculation and dewatering of a waste-activated biological sludge is discussed below.

Waste-activated sludges are common in municipal wastewater treatment applications. They often contain substantial amounts of suspended fine material arising from the bacterial population. High-molecular weight cationic polymers are often used to flocculate such suspensions, and it has been seen that when such polymers are made with the incorporation of low levels of branching agents that the performance may be greatly enhanced (16, 20), especially when the flocculated suspensions are dewatered using a centrifuge. In order to obtain a better understanding of this phenomenon, a series of structured (i.e. long-chain branched) poly(acrylamide$_{60}$-co-AETAC$_{40}$) copolymers (AETAC = 2-(acryloyloxy)ethyltrimethylammonium chloride) incorporating different amounts of the branching agent N,N'-methylenebisacrylamide (MBA) were synthesized in inverse emulsion formulations.

A metric for the degree of branching was devised based on the amount of the centrifugally sedimentable fraction of the polymer (isolated from the emulsion formulation components) as a function of NaCl concentration in aqueous solution (16). Polymer concentrations (~ 500 ppm), in NaCl solutions ranging from 1 mM to 1 M, before centrifugation and in the supernatant after centrifuging for 1 hr at 13 Krpm were determined from UV absorbances at 215 nm. The sedimentable fraction is reported as a relative change in the UV absorbance (ΔUV) upon centrifugation as a function of NaCl concentration. Linear high-molecular weight copolymers (no added MBA) resulted in no sedimentable fraction over the entire range of NaCl concentrations under the centrifugation conditions employed. Small amounts of branching agent, equivalent to average addition rates of a few MBA molecules per chain, produced measurable amounts of a sedimentable fraction, which increased regularly with salt concentration and MBA content. The efficacies of these polymers for waste-activated sludge dewatering were determined as the volumes of water draining in 10 sec from 200 g of 1% sludge suspensions mixed for 5 sec at 1000 rpm (flat blade impeller in a square container) with various doses of diluted (0.2%) polymer solutions. Polymer doses are given as weight polymer per dry weight of waste-activated sludge.

The figures below show the metric for degree of polymer branching (ΔUV vs. [NaCl] curves), and the dewatering performance in waste-activated sludge

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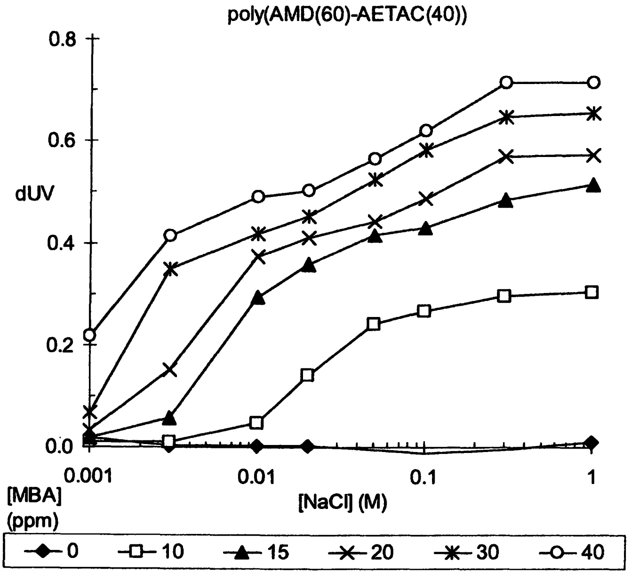

Figure 4. Sedimentation-salinity profiles for various poly(acrylamide$_{60}$-AETAC$_{40}$) copolymers structured with MBA

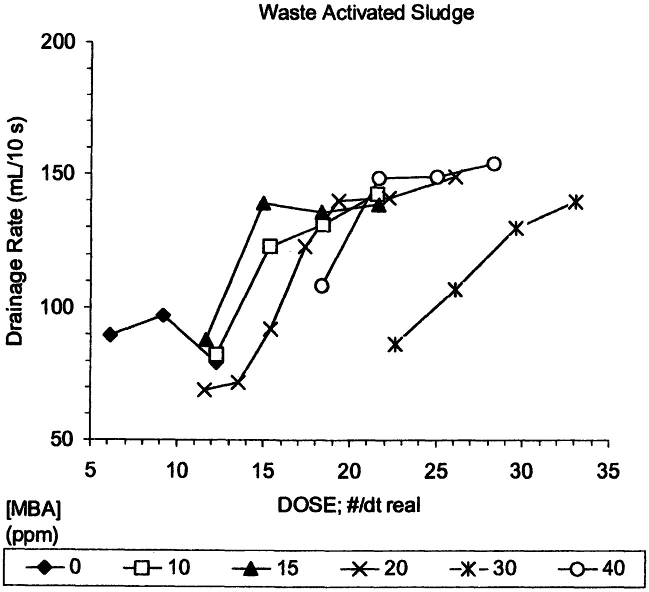

Figure 5. Dewatering performance of samples in Figure 4

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(drainage rate vs. polymer dose). Clearly there was an optimal degree of polymer structuring where the performance (dewatering rate) improved with only a minor dose penalty. For greater degrees of structuring the performance remained unchanged and the effective dose increased. This crossover point occurred when the polymer sample exhibited a sedimentable fraction at the lowest salinity. We interpreted this low-salinity sedimentable fraction as a highly ineffective component in this flocculation and dewatering application.

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Summary

The solution of many practical problems and the basis for a substantial number of technologies involving aqueous systems relies on employing polyelectrolytes in a useful manner. The bridge between empirical wisdom obtained from work on complex practical systems and fundamental principles can be built from a good understanding of the physical and chemical phenomena underlying the system and the application.

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